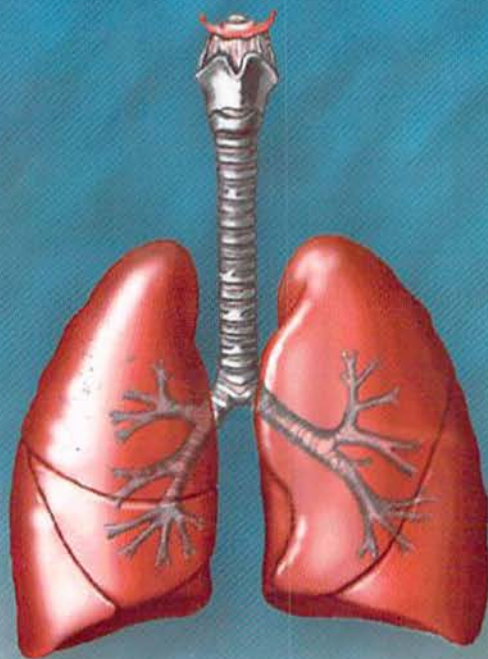


Human

PHYSIOLOGY

for medical students



RESPIRATION

MAGDI SABRY M.D.

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**HUMAN
PHYSIOLOGY
FOR MEDICAL STUDENTS**

RESPIRATION

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DEDICATED TO

MY TEACHERS THROUGHOUT MY LIFE, particularly the first 2 teachers, my late parents.

MY FAITHFUL LATE WIFE, the light that disappeared from life but is everlasting inside me.

MY SONS, SHERIF, AMR AND ESSAM, AND THEIR WIVES, their love gives me hope and interest in life and makes their happiness my chief goal.

MY GRANDCHILDREN, AHMED, NOURHAN AND SAMA SHERIF, YASMIN AND MOHAMMED AMR, AND AYA ESSAM, the beautiful young angels that have added a new kind of happiness to my life.

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PREFACE

With recent advances in the field of human physiology, it has become urgent to provide an up to date review on the subject.

This book is provided to help medical students in understanding modern human physiology. It presents the whole subject in a brief, comprehensive, and up to date form.

Great effort was done to perfect such a vast subject in an easily understandable expression and in a such reasonable bulk. It includes as much simplified and clear illustrations as possible, and to maintain simplicity, they have been presented in a diagrammatic form, photographs were greatly excluded.

The major part of my gratitude should be given to all who taught me, and to my wife and children who, patiently, supported me during preparation of this book.

Any suggestions, remarks or criticism will be greatly welcomed, heartily appreciated and very much considered.

I hope this book will be a real help to undergraduate medical students, as well as to postgraduates and candidates of higher degrees, in the field of human physiology.

MAGDI SABRY
1986

Second edition : 1990

Third edition : 1994

Fourth edition : 1999

Preface to the fifth edition

This new edition is original both in shape and contents. All chapters have been extensively revised and updated. Recent data are added elsewhere and many subjects have been completely rewritten.

MAGDI SABRY
2006

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CHAPTER 1

THE RESPIRATORY SYSTEM

DEFINITION & DIVISIONS OF RESPIRATION

The term respiration refers to the processes involved in the supply of the tissue cells with O_2 as well as the elimination of the produced CO_2 . During rest, the O_2 consumption in a normal young adult individual averages 250 ml / minute, while the CO_2 production averages 200 ml / minute. In man, the process of respiration is divided into 3 stages :

(1) External respiration (pulmonary respiration)

This is the uptake of O_2 and excretion of CO_2 in the lungs. It includes the following 2 processes :

A- Pulmonary ventilation

This is the process of aeration (= renewal of air) of the lungs. It occurs through the **breathing movements** which include *inspiration and expiration*. Such movements occur in cycles called the **breath or respiratory cycles**, each of which consists of *one inspiration and one expiration followed by a short expiratory pause*. These cycles result in continuous inflow of air from the atmosphere into the lung's alveoli and outflow of air in the opposite direction. Their frequency during rest is normally high in newly born infants (40 per minute or more), but it gradually declines during childhood, and in young adult individuals, *the breathing rate is 12–16 per minute*.

B- Pulmonary gas exchange

This is the process of O_2 diffusion from the alveolar air into the pulmonary capillaries, and the diffusion of CO_2 in the opposite direction.

(2) Transport of gases (O_2 and CO_2)

This is carried out by the blood, which transports O_2 from the lungs to the tissues and CO_2 in the opposite direction.

(3) Internal respiration (or tissue respiration)

This includes the process of gas exchange between the tissue cells and their fluid medium as well as the processes involved in the utilization of O_2 and production of CO_2 by the cells.

THE RESPIRATORY SYSTEM (OR APPARATUS)

The respiratory system consists of the following structures :

1. The respiratory tract (= the airways or passages) and the lungs (figure 1).
2. The thoracic cage and respiratory muscles.
3. The nerve centres that control the respiratory muscles, as well as the tracts and nerves that mediate such control (see later).

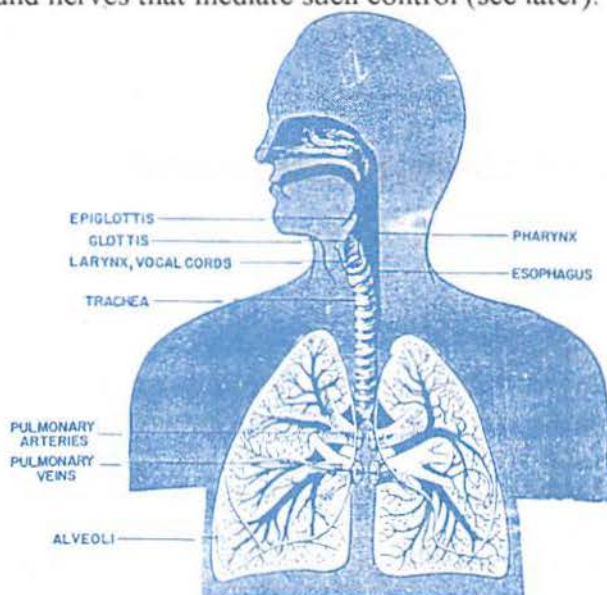


Figure 1 : The respiratory system.

THE AIR PASSAGES (OR AIRWAYS)

These are divided into *upper and lower parts*. The upper passages include the nasal cavities and the 3 parts of the pharynx (the nasal , oral and laryngeal parts), while the lower passages include the larynx and the trachea as well as the bronchi and the bronchioles.

The trachea and bronchial tree

In adults, the trachea is 10-12 cm long and 1.6-2 cm wide. The larynx is present at its upper end, while at its lower end it bifurcates into 2 large bronchi, one for each lung. Each bronchus divides in the corresponding lung into progressively narrower and thinner *bronchi*, which in turn divide into

still smaller tubes called the *bronchioles*. This system simulates a branching tree, so it is frequently called *the bronchial tree* (figure 2 left). The bronchial diameter is generally more than 1.5 mm, while that of the bronchioles is less than 1.5 mm.

There are 20-25 (average 23) generations of branching in the bronchial tree. In the first 16 generations, gas exchange does not occur, and they only conduct air into and out of the lungs. The 16th generation consists of small *terminal bronchioles*, the diameter of which is about 1 mm. The latter branch into smaller *respiratory bronchioles*, which have a diameter of about 0.5 mm and occupy the 17th, 18th and 19th generations of the bronchial tree. Each respiratory bronchiole divides into several *alveolar ducts*, each of which leads to several *atria*, which conduct air to the *alveolar sacs and alveoli* (figure 3), and all these parts occupy the last 4 generations of the bronchial tree (figure 2 right).

The multiple dividing of the bronchial tree greatly increases the cross-sectional area of the small airways (*from 2.5 cm² in the trachea to about 11800 cm² in the alveoli*), and also results in marked reduction of the air-flow velocity in these airways.

Functionally, the bronchial tree is divided into 3 zones (figure 2 right) :

1. **Conduction zone** : This extends from the trachea down to the terminal bronchioles (the 16th generation of the bronchial tree). It receives blood supply from the *bronchial arteries* (which are branches from the aorta) and since no gas exchange occurs in this zone, it is called the *anatomic dead space* (see later).
2. **Transition zone** : This consists of the *respiratory bronchioles* (the 17th, 18th and 19th generations of the bronchial tree). It conducts air and *also allows some gas exchange* because these bronchioles contain some alveoli in their walls.
3. **Respiratory zone** : This includes the alveolar ducts, atria and alveolar sacs, and it receives blood supply from the *pulmonary arteries*. It is the *main site of gas exchange*, which occurs in the alveoli. The latter are *located mainly in the alveolar sacs*, and few are also present in the alveolar ducts and respiratory bronchioles (see above).

Chapter 1

The respiratory system

The trachea and large bronchi are kept open by *incomplete cartilagenous rings* in their walls. There are also cartilagenous plates in the walls of the smaller bronchi, but they become progressively less in the later generations of bronchi, and are almost absent in the bronchioles.

The walls of the tracheobronchial tree also contain smooth muscle fibres (which are few in the trachea and large bronchi but abundant in the bronchioles, specially the *terminal bronchioles*). These muscle fibres *relax by sympathetic stimulation* (resulting in bronchodilatation) and *contract by parasympathetic stimulation* (resulting in bronchoconstriction).

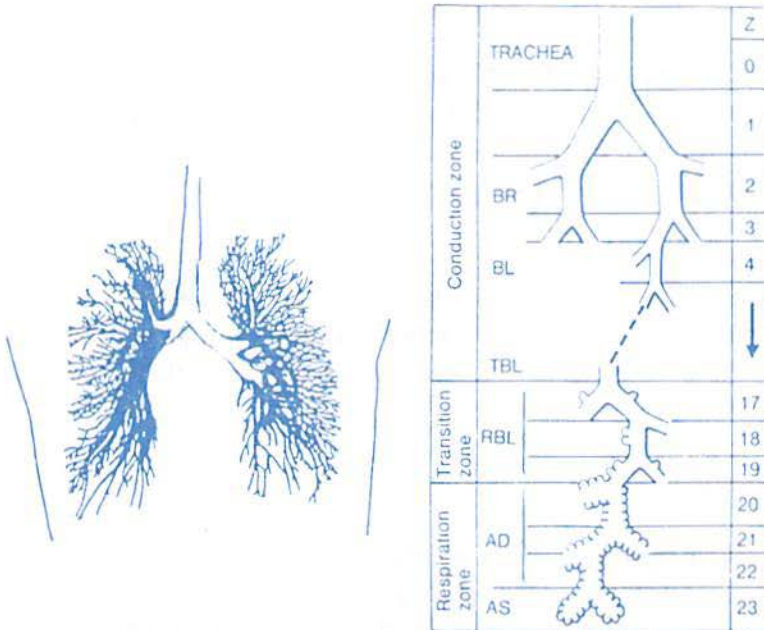


Figure 2 : X-ray photograph of the bronchial tree (left), and its anatomical and functional divisions (right). Z = Generation number. BR = Bronchi. BL= Bronchioles. TBL= Terminal bronchioles. RBL= Respiratory bronchioles. AD = Alveolar ducts. AS = Alveolar sacs.

The inner walls of the tracheobronchial tree are lined by mucous membranes consisting of *ciliated columnar epithelial cells* (about 200 cilia on each cell). In the trachea and large bronchi, these membranes contain *goblet cells* as well as submucosal *mucous & serous glands*, the secretion of which is stimulated by parasympathetic stimulation (but these glands are almost absent in the bronchiolar walls). Cilia are present till the beginning of the respiratory bronchioles, and they *beat upwards* at a rate of 1000-1200 times/minute (which drives mucus and foreign particles towards the pharynx at a velocity of 10-16 mm/minute to be eliminated). This mechanism is called *ciliary escalator*, and if it is defective e.g. congenitally (= *Kartagener's syndrome*), it leads to chronic sinusitis and recurrent lung infection.

THE LUNGS

The lungs contain the bronchial trees, and their main bulk is made up by the *respiratory zones of these trees* in addition to a *very rich blood supply from both the pulmonary arteries and the bronchial arteries* (see above). They are formed of **lobes** (3 in the right lung and 2 in the left lung), each of which consists of a large number of **lobules**.

The lung lobule receives *one terminal bronchiole*, which subsequently divides into several **respiratory bronchioles**. Each respiratory bronchiole then divides into several **alveolar ducts**, each of which leads to many **atria**. The **alveolar sacs** open at these atria, and their walls are composed entirely of the **alveoli**. Each respiratory bronchiole and its related alveolar ducts, atria, air sacs and alveoli, constitute *a respiratory unit* (figure 3).

Normally, there is a thin layer of fluid between the lungs and chest wall in the pleural cavity (page 6) which *facilitates free sliding* of the lungs on the chest wall and also *keeps them in close contact with each other* (in the same way that 2 moist pieces of glass slide on each other but resist separation).

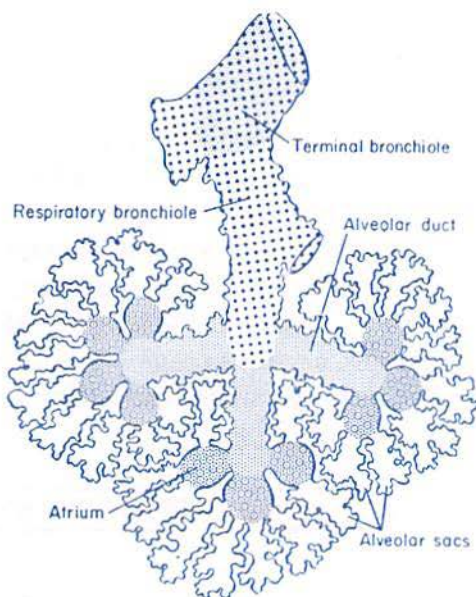


Figure 3 : The respiratory unit.

The lung alveoli

These are the site of gas exchange in the lungs. There are about **300 million alveoli in both lungs** that have a total surface area of **70-80 square meters**, and the diameter of each alveolus is 0.2-0.3 mm. The alveolar walls are formed of *a single layer of flat epithelial cells* that are surrounded by an *extensive network of pulmonary capillaries*. Gas exchange occurs across this *alveolo-capillary membrane*, the thickness of which is only about **0.6 micron**, which allows easy diffusion of gases.

The alveolar epithelial cells are 2 types : (a) **Type I cells** : These are flat cells that constitute the main lining cells. (b) **Type II cells (= granular pneumocytes)** : These are much less in number, and they secrete an important substance called **surfactant** (page 33). The subepithelial tissue contains lymphocytes, plasma cells and mast cells while large phagocytic cells called **dust cells or pulmonary alveolar macrophages (PAM)** are present in the alveolar cavities.

The pulmonary interstitial tissue contains **elastin and collagen fibres**, which are elastic fibres that allow both distension and recoil of the lungs. The alveoli are also lined by *a very thin film of fluid*, and the surface tension that develops in this film resists excessive alveolar distension and increases the recoil forces in the lungs (page 32).

The pleural sac (pleura)

Each lung is surrounded by a closed thin serous sac called the pleural sac. This sac has 2 layers : (a) An inner layer called the **visceral pleura**, which covers the surface of the lung. (b) An outer layer called the **parietal pleura**, which lines the inner surface of the thoracic cage and the mediastinum, as well as the upper surface of the diaphragm.

There is a potential space between the 2 layers (= *the pleural cavity*) the pressure in which is normally **negative** (page 32). It contains *only a thin film of serous fluid*, which acts as a **lubricant** that facilitates the lung movements within the thoracic cavity.

FUNCTIONS OF THE RESPIRATORY SYSTEM

(A) Respiratory function

This is the uptake of O_2 from the surrounding atmosphere and the elimination of CO_2 to it. Such function is performed by the **respiratory and transition zones of the respiratory passages** (see above).

(B) Non-respiratory functions

- (1) The breathing movements (i.e. inspiration and expiration) affect the *rates of venous return and lymph flow* (refer to circulation).
- (2) The *venous blood is filtered in the pulmonary capillaries*, so that no blood clots or other emboli would reach the arterial blood.
- (3) By controlling the rate of CO₂ excretion, the respiratory system plays a basic role in the *regulation of the acid-base balance* (refer to kidney).
- (4) The *volatile waste products other than CO₂ (e.g. acetone) are excreted via the respiratory system* (more than 250 different volatile substances have been identified in the human breath).
- (5) The lungs perform several *metabolic & endocrine functions* (see below)
- (6) The *conducting zone of the respiratory passages* performs the following *non-respiratory functions* :
 - a- *Perception of smell sensation* by the olfactory mucosa in the nose.
 - b- *Phonation or vocalization* (by supplying air to the larynx).
 - c- *Regulation of the body temperature* (by helping heat loss through water evaporation from the respiratory mucous membranes).
 - d- Adjusting the air flow resistance (by *controlling the bronchial tone*).
 - e- Providing *many protective (defense) mechanisms* (see next).

THE RESPIRATORY PROTECTIVE MECHANISMS

The following "*lung defense mechanisms*" operate together to protect the *delicate alveoli* from both infection as well as damage.

(A) Role of the alveoli : Foreign particles that reach the alveoli (e.g. dust and the microorganisms less than 2 microns in diameter) are attacked and phagocytosed by the *pulmonary alveolar macrophages* (see above).

(B) Role of the respiratory passages :

- 1- **Air conditioning** : This means *humidification of the inspired air and adjusting its temperature to equal that of the body*. This process protects the pulmonary epithelium and alveoli from damage that can be produced by too dry and too cold or hot air.
- 2- The bronchial secretion contains *immunoglobulins* which are antibodies that resist infections & maintain the integrity of the resp. mucosa.
- 3- **Trapping and elimination of large foreign particles**: Particles more than 10 microns in diameter are trapped by hair at the nostrils then eliminated by the *sneeze reflex* (see below). Some of these particles also

impact on the *tonsils and adenoids*, which are immunologically-active collections of lymphoid tissue. On the other hand, particles 2-10 microns in diameter stick to the mucus that lines the trachea and bronchi then eliminated by the *cough reflex* (see below).

The nasal and bronchial secretions are directed *towards the pharynx* by the *ciliary movement*, where they are either eliminated outwards in the form of *sputum*, or swallowed (and in the stomach most bacteria are killed by the HCl secreted by the gastric mucosa).

The cough reflex

This is a protective reflex that is initiated by irritation of the larynx, trachea or bronchi. The stimulus excites certain *mucosal rapidly-adapting irritant receptors* that discharge signals via *afferent vagal nerve fibres* to the respiratory centres in the brain stem, leading to coughing.

Coughing starts by a short inspiration (about 2.5 litres of air), then the glottis is closed by the epiglottis and approximation of the vocal cords. This is followed by a forcible expiration, which increases the pressure of the trapped air in the lungs to about 100 mmHg. The glottis is then suddenly opened, so the air in the lungs is expelled at a high velocity (75-100 miles per hour) which drives the irritant substance out.

In addition to producing coughing, laryngeal irritation also causes reflex contraction of the laryngeal muscles (= *laryngeal spasm reflex*) which also prevents entrance of foreign or irritant bodies into the trachea.

The sneeze reflex

This is a protective reflex initiated by irritation of the nasal mucosa. The stimulus excites certain *nasal irritant receptors* that discharge signals via *afferent trigeminal nerve fibres* to the respiratory centres in the brain stem, leading to sneezing.

Sneezing starts by a short inspiration followed by a forced expiration while *the glottis is kept open*. The uvula is depressed and the rapidly moving expired air expels the irritant substance in the nasal passages outwards.

Functions of the nose

- 1- Warming and humidification of the inspired air.
- 2- Trapping of foreign particles larger than 10 microns in diameter.
- 3- Initiation of the sneezing reflex.
- 4- Perception of the sensation of smell (refer to special senses).

Functions of the larynx

In addition of being a part of the air passage, the larynx is also concerned with **vocalization or phonation** (sound production). This is produced as a result of **vibrations of the vocal cords** while air is passing out of the lungs by a voluntary expiratory effort, and the pitch of the sound is determined by the frequency of vibration of these cords. Such frequency in turn depends on the tightness of the vocal cords as well as their shape and mass of edges. All these changes in the vocal cords are produced by activity of the laryngeal muscles, which are voluntary muscles supplied by the vagi nerves.

Metabolic and endocrine functions of the lungs

- 1- The type II alveolar epithelial cells secrete the **surfactant** for local use.
- 2- The lungs **synthesize certain substances and release them into the blood** e.g. some prostaglandins, histamine and kallikrein.
- 3- The lungs partially **remove certain substances** from the blood e.g. serotonin, bradykinin, acetylcholine, norepinephrine and some prostaglandins.
- 4- The lungs contain **a fibrinolytic system** that lyses blood clots in the pulmonary vessels.
- 5- **Heparin** is secreted by the mast cells (which are abundant in the lungs).
- 6- Angiotensin I is converted to angiotensin II mainly in the lungs by activity of the ACE (**Angiotensin-converting enzyme**). This enzyme is located in small pits called **caveolae** on the vascular surface of the pulmonary capillary endothelial cells, and it also **inactivates bradykinin**.
- 7- VIP (Vasoactive intestinal polypeptide) is secreted in the lungs, probably by the **nonadrenergic-noncholinergic nerves** that cause relaxation of the bronchial smooth muscle (see next).

The bronchial tone

The bronchial tone is produced by activity of the bronchial musculature and its main function is to maintain an equal distribution of ventilation in the lungs. It normally shows a **circadian rhythm** with maximal constriction (i.e. parasymp. activity) at 6 AM and maximal dilatation (i.e. symp. activity) at 6 PM (so asthmatic attacks are more severe at late night and early morning).

The bronchial muscles receive both **symp. and parasymp. nerve fibres** as well as **nonadrenergic-noncholinergic nerves**. The latter produces bronchodilatation and VIP is probably the responsible mediator. These muscles contain **muscarinic cholinergic as well as beta 1 & 2 adrenergic receptors**

(the *beta 2* type predominates in humans). Parasympathetic stimulation produces bronchoconstriction and increases the bronchial secretion (by acting on the muscarinic receptors), while sympathetic stimulation produces bronchodilatation and decreases the bronchial secretion (by acting on the beta receptors), so the *beta-stimulator drugs are used for relieving acute asthmatic attacks*.

Some nerves in the lungs also contain *substance P*, which produces bronchoconstriction and increases the secretion of mucus.

The following table shows *the various agents that affect the bronchial tone* :

CAUSES OF BRONCHOCONSTRICTION	CAUSES OF BRONCHODILATATION
Cholinergic drugs e.g. <i>acetylcholine</i>	Muscarinic receptors blockers e.g. <i>atropine</i>
Beta-adrenergic receptors blockers e.g. <i>propranolol</i>	Beta-adrenergic receptor stimulators e.g. <i>isoproterenol and salbutamol</i>
Histamine and leukotrienes	Vasoactive intestinal polypeptide (VIP)
Tachykinins (specially <i>substance P</i>)	Certain prostaglandins
Cool air and muscular exercise	
Certain irritants and chemicals e.g. <i>SO₂</i>	

ASTHMA

This is a disease characterized by extremely-difficult breathing due to *airway obstruction*. Its usual cause is *allergic hypersensitivity* to a foreign substance (= antigen or allergen) in air (commonly plant pollens). The lungs of the patient contain large amounts of immunoglobulins (Ig) i.e. *antibodies against that antigen* (specially IgE) that are attached to the *mast cells*. On inhaling the antigen, an antigen-antibody reaction is initiated and causes the mast cells to release substances that cause spasm of the bronchial muscle, localized inflammatory edema in the bronchial walls and secretion of thick mucus (all these effects lead to bronchial obstruction and increase the airway resistance). Of these substances are *histamine and slow-reacting substance of anaphylaxis* (the latter is a mixture of *leukotrienes*). In some cases, there is also *deficiency of VIP or excess release of substance P*.

Breathing is difficult *mainly during expiration* because the already constricted bronchioles are also compressed in the deflating lungs. The attacks are more severe in the late night and early morning and are *treated by beta adrenergic receptors stimulators and muscarinic receptors blockers* (see the table above) as well as by *anti-histaminic drugs and glucocorticoids* (the latter depress the allergic response).

EMPHYSEMA

This is a degenerative lung disease characterized by loss of the lung's elasticity and breakdown of the alveolar walls (so the alveoli are replaced by large air sacs). Its commonest cause is *heavy cigarette smoking*. The smoke *increases the number of the PAMs* (= pulmonary alveolar macrophages), which release a chemical substance that *attracts the leukocytes* to the lungs, and these secrete (a) *The elastase enzyme*, which attacks the elastic tissue in the lungs (b) *O₂ radicles*, which *block the action of a protein in the plasma called alpha 1 antitrypsin that normally inactivates the elastase enzyme*.

In about 2 % of cases, *there is congenital deficiency of antitrypsin 1*, and smoking in such cases leads to a severe kind of emphysema early in life.

EFFECTS OF SMOKING

- 1- Predisposition to lung infection and emphysema (see above) as well as lung cancer.
- 2- Irritation and damage of the respiratory mucosal epithelium.
- 3- Inhibition of the ciliary movement.
- 4- Decreased secretion of the surfactant (page 33).
- 5- Less release of antibodies from the plasma cells.
- 6- Inefficient gas exchange in the lungs.
- 7- Delivery of harmful substances into the body specially carbon monoxide.

CHAPTER 2

THE LUNG VOLUMES AND CAPACITIES

THE LUNG VOLUMES

A lung volume is a subdivision of the total capacity of the lungs. They are measured when the lungs are in the *midthoracic position* (at the end of a normal resting expiration). Their values normally vary with age and sex, being 20-25 % less in females, and even more in old age except the residual volume (see below). The various lung volumes and their average normal values in young adult males include the following (figure 4) :

1- TIDAL VOLUME (TV)

This is the volume of air that moves into the respiratory passages (i.e. inspired or expired) in a single breath cycle during *eupnea* (= normal resting quiet breathing). *The average TV is 500 ml.*

2- INSPIRATORY RESERVE VOLUME (IRV)

This is the volume of air that can be inspired by a maximal inspiratory effort (i.e. by the deepest possible inspiration) *after the end of a normal resting inspiration* (i.e. in excess of the TV). *The average IRV is 3000 ml.*

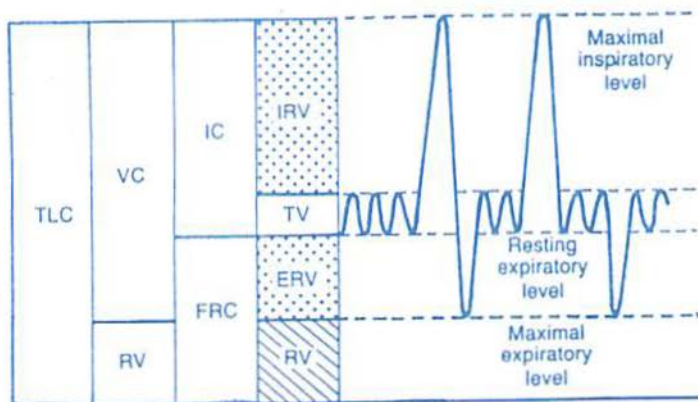


Figure 4 : A normal spirogram showing the various lung volumes & capacities.

3- EXPIRATORY RESERVE VOLUME (ERV)

This is the volume of air that can be expired by a maximal expiratory effort (i.e. by the deepest possible expiration) *after the end of a normal resting expiration* (i.e. in excess of the TV). *The average ERV is 1000 ml.*

4- RESIDUAL VOLUME (RV)

This is the volume of air that *remains in the lungs after the end of a maximal expiration*. Its average value is *1200 ml*, and it can be expelled out of the lungs *only after their collapse* (e.g. after opening of the chest).

The minimal air (or volume) and its clinical importance

After opening of the chest, however, about 150 ml of air still remain in the lungs. This is called *minimal air or volume*, and it is *used medicolegally* in detecting *whether a newly born dead baby had died before or after delivery*. This is known by placing a piece of the baby's lung in water. If it floats, it indicates presence of the minimal air (i.e. the baby was born alive and breathed then died). On the other hand, if it sinks, it indicates absence of the minimal air (i.e. the baby was born dead and had never breathed).

THE LUNG CAPACITIES

A lung capacity comprises *2 or more lung volumes*. The various lung capacities and their average normal values in *young adult males* include :

1- INSPIRATORY AND EXPIRATORY CAPACITIES (IC & EC)

The IC is the volume of air that can be inspired by a *maximal inspiratory effort after the end of a normal resting expiration*. It equals the $TV + IRV =$ about *3500 ml*. On the other hand, the EC is the volume of air that can be expired by a *maximal expiratory effort after the end of a normal resting inspiration*. It equals the $TV + ERV =$ about *1500 ml*.

2- FUNCTIONAL RESIDUAL CAPACITY (FRC)

This is the volume of air that *remains in the lungs after the end of a normal resting expiration*. It equals the $ERV + RV =$ about *2200 ml*.

3- VITAL CAPACITY (VC)

This is the volume of air that can be expelled out by *a maximal expiration after a maximal inspiration*. It equals the $TV + IRV + ERV =$ about 4500 ml. However, it *normally varies with the size of the body*. Accordingly, its measured value must be predicted relative to the body surface area. Normally, it averages 2500 ml and 2000 ml per square meter of body surface area in young adult males and females respectively.

4- TOTAL LUNG CAPACITY (TLC)

This is the *volume of air that the lungs contain after a maximal inspiration*. It includes *all lung volumes* ($TV + IRV + ERV + RV$) or, in other words, it equals the $VC + RV =$ about 5700 ml.

FACTORS THAT AFFECT THE VITAL CAPACITY (VC)

- 1- **Posture** : The VC is greater in the standing or sitting positions than in the recumbent position, *because in the latter position the lung capacity is decreased* due to 2 factors (a) The viscera press on the diaphragm (which limits its descent). (b) The blood volume in the lungs increases (because the venous return increases as a result of loss of the effect of gravity).
- 2- **Movement of the diaphragm** : Conditions that limit the diaphragmatic descent (e.g. *pregnancy and ascites*) decrease the VC specially in the recumbent position (see above).
- 3- **Pulmonary blood volume** : Pulmonary congestion (= increased blood volume in the lungs) e.g. *in left ventricular failure*, decreases the VC specially in the recumbent position (see above).
- 4- **Strength of the respiratory muscles** : The VC is greater in athletes than in sedentary people, and is decreased in all muscle diseases, myasthenia gravis, and diseases associated with paralysis (e.g. poliomyelitis).
- 5- **Lung compliance (stretchability)** : A decrease in the lung compliance reduces the VC. This commonly occurs in (a) *Lung fibrosis* [e.g. after a severe TB (tuberculosis) infection]. (b) *Pneumothorax* (collection of air in the pleural sac) (c) *Hydrothorax* (collection of fluid in the pleural sac).

- 6- **Lung elasticity** : Reduction of the elastic property of the lungs decreases the VC e.g. in *emphysema* (page 11), in which the lungs are well inflated and their *compliance increases*, but expiration becomes difficult.
- 7- **Resistance to air flow** : An increase in the resistance to air flow reduces the VC. This occurs in *obstructive lung diseases e.g. asthma*, in which the resistance to air flow occurs mainly during expiration (page 10).
- 8- **Expansibility of the thoracic wall** : A decrease in the expansion of the thorax reduces the VC. This commonly occurs due to deformities in either the thoracic cage or the vertebral column (e.g. kyphosis and scoliosis).

****** The diseases that limit the lung or thoracic wall expansibility are called *restrictive lung diseases*. In these diseases, as well as in cases of pulmonary congestion and limited diaphragmatic movement, *both the TLC as well as the VC are reduced*. On the other hand, in diseases characterized by difficult expiration (e.g. emphysema and asthma), *the TLC is almost normal while the VC is decreased and the RV is increased*.

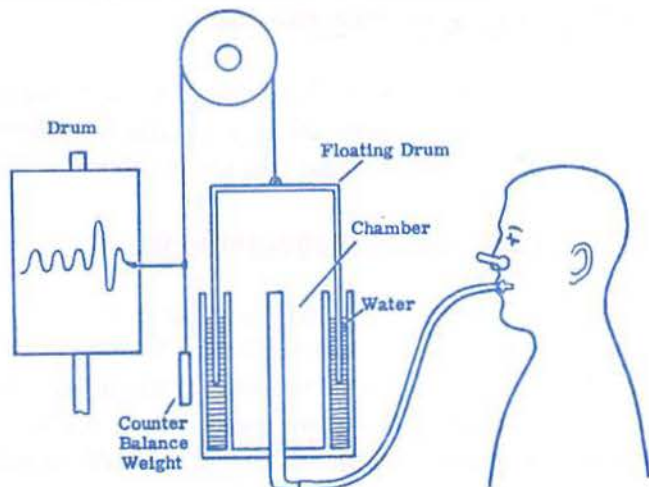


Figure 5 : The spirometer and a spirogram recorded on a drum

MEASUREMENT OF THE LUNG VOLUMES AND CAPACITIES

The lung volumes already described are called *static volumes*, because they are measured while the subject is in the resting midthoracic position. All can be measured by an apparatus called the *spirometer* (figure 5) *except the residual volume*. Therefore, the capacities that include the residual volume (i.e. FRC and TLC) *cannot be measured by this apparatus*.

Measurement of the residual volume (RV)

The RV can be measured by application of the *dilution principle* as follows. The subject expires maximally (so only the RV remains in the lungs)

then he breathes deeply 3 - 4 times *in a spirometer that contains a known concentration of helium in air*. In this way, helium is diluted by the RV and its concentration becomes equal in both the spirometer air and the RV. The *amount of helium remains constant during the test* because (a) It is present in a closed circuit (b) It is an *inert gas* that is not produced or utilized by the body (c) It is almost *insoluble in the blood*. After equilibration, the RV is calculated as follows :

- 1- *The amount of helium before equilibration* = volume of air in the spirometer (V_1) $\times$ helium concentration in that air (C_1).
- 2- *The amount of helium after equilibration* = ($V_1 + RV$) $\times$ final helium concentration in the spirometer air (C_2).

Since both (1) and (2) are equal (i.e. $V_1 C_1 = (V_1 + RV) C_2$), then mathematically, the $RV = \frac{V_1 (C_1 - C_2)}{C_2}$.

Clinical importance of measuring the RV

Normally, the RV is less than 30 % of the TLC. Such ratio is exceeded in diseases that cause *inefficient expiration*, particularly *asthma & emphysema*, and ratios more than 35 % indicate that the condition is serious .

Importance of the FRC and its measurement

The FRC maintains an adequate gas exchange in the lungs in the intervals between breaths, and its large volume (about 5 times the TV) prevents acute changes in the O_2 and CO_2 concentrations in the blood. It can also be measured by using *the dilution principle* (see above), but in this case *the subject starts breathing in the spirometer after a normal expiration*.

DIFFERENCES BETWEEN ALVEOLAR AND EXPIRED AIR

The alveolar air is that air that undergoes gas exchange with blood in the pulmonary capillaries. Its volume is about **2000 ml** after a quiet expiration. It continuously loses O_2 and gains CO_2 , so its O_2 content is less and its CO_2 content is more than the amounts of these gases in both the inspired and the expired air (see the table below).

During inspiration, the air conducting part of the respiratory passages (which is called the *anatomical dead space*) contains *atmospheric air*. However during the next expiration, this air is exhaled first and is followed by alveolar air (which *fills the anatomical dead space after expiration*). There-

fore, the expired air is a mixture of alveolar air and atmospheric air from the anatomical dead space.

The following table shows the composition of the inspired, expired and alveolar air, all fully saturated with water vapour (PP = partial pressure in mmHg).

	CO ₂		O ₂		N ₂ & inert gases		water vapour	
	%	PP	%	PP	%	PP	%	PP
Inspired air	0.04	0.3	19.6	149	74.16	563.7	6.2	47
Expired air	3.7	28	15.8	120	74.3	565	6.2	47
Alveolar air	5.3	40	13.1	100	75.4	573	6.2	47

** The partial pressure of O₂ in dry air is 160 mmHg (see page 59).

THE RESPIRATORY DEAD SPACE (DS)

This is the space in the respiratory system *occupied by gas that does not exchange with blood*. It is subdivided into the following types :

1. Anatomical DS : This is the area in which gas exchange *does not normally occur*. It extends from the nose down till the respiratory bronchioles, and its volume is normally *about 150 ml*.

2. Alveolar DS : This includes the alveoli in which no gas exchange occurs due to blockage of their blood supply. It is *normally absent (= zero)*.

3. Physiological DS : This is the area of *wasted ventilation* in the respiratory system (i.e. the area in which no gas exchange occurs). *It equals the sum of the anatomical and alveolar dead spaces*. Since normally no alveolar dead space exists, *the physiological DS should be normally equal to the anatomical DS*.

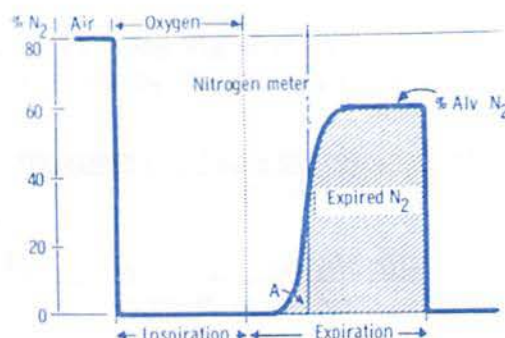


Figure 6 : Measurement of the anatomical DS by Fowler's method.

MEASUREMENT OF THE ANATOMICAL DS

The anatomical DS is measured by Fowler's method. This method is based on analysis of *a single breath nitrogen curve*. The subject inhales a deep breath of *pure O₂*, then he expires slowly and the expired air volume is recorded by a flow meter while its N₂ content is measured by a nitrogen meter (figure 6). The initial volume of expired air is derived from the anatomical DS, and it contains only O₂ and no N₂. This is followed by a mixture of air from both the dead space and the alveoli, in which the N₂ concentration rises gradually (area A in the curve), then by pure alveolar air, in which the N₂ concentration reaches a maximum. From the curve in figure 6, *the anatomical DS = volume of expired air between the 2 vertical lines*.

MEASUREMENT OF THE PHYSIOLOGICAL DS

The physiological DS is measured by Bohr's method (equation). This method is based on the fact that the *CO₂ in the expired air is derived entirely from the alveolar air and not from the DS* (because after inspiration the DS is filled with atmospheric air, which normally contains a negligible amount of CO₂). Therefore, *the amounts of CO₂ in the whole expired air volume as well as in its part that is derived from alveolar air are equal*, and each = its volume x its CO₂ %, i.e.

$$\text{Expired air volume} \times \text{its CO}_2 \% = \text{Alveolar air volume} \times \text{its CO}_2 \%$$

Since the expired air volume = tidal volume (TV), and its part that is derived from alveolar air = expired air volume - DS (i.e. TV - DS) then :

$$\begin{aligned} TV (\text{CO}_2 \% \text{ in exp. air}) &= (TV - DS) \text{CO}_2 \% \text{ in alv. air} \\ &= TV (\text{CO}_2 \% \text{ in alv. air}) - DS (\text{CO}_2 \% \text{ in alv. air}). \end{aligned}$$

By shifting,

$$\begin{aligned} DS (\text{CO}_2 \% \text{ in alv. air}) &= TV (\text{CO}_2 \% \text{ in alv. air}) - TV (\text{CO}_2 \% \text{ in exp. air}) \\ &= TV (\text{CO}_2 \% \text{ in alv. air} - \text{CO}_2 \% \text{ in exp. air}) \end{aligned}$$

$$\text{Therefore, } \frac{DS}{TV} = \frac{\text{CO}_2 \% \text{ in alv. air} - \text{CO}_2 \% \text{ in exp. air}}{\text{CO}_2 \% \text{ in alv. air}} \quad \text{and,}$$

$$DS = TV \times \frac{\text{CO}_2 \% \text{ in alv. air} - \text{CO}_2 \% \text{ in exp. air}}{\text{CO}_2 \% \text{ in alv. air}}$$

Since the partial pressure (P) of a gas is proportionate to its concentration, the *P_{CO2} can be used instead of the CO₂ %*, and the above relation becomes

as follows (= **Bohr's equation**) :

$$DS = TV \times \frac{P_{CO_2 \text{ in alv. air}} - P_{CO_2 \text{ in exp. air}}}{P_{CO_2 \text{ in alv. air}}}$$

****** Pure alveolar air is difficult to obtain, and the last few ml of the expired air are usually used instead. However, since *the alveolar air and arterial blood are normally in equilibrium*, the P_{CO_2} in both is equal, and accordingly, in Bohr's equation, *the P_{CO_2} in the arterial blood (which is easy to measure) can be used instead of the P_{CO_2} in the alveolar air.*

FUNCTIONS AND SIGNIFICANCE OF THE ANATOMICAL DS

- (1) The DS constitutes *the conducting part of the respiratory tract*, which performs the following functions (also see pages 7 & 8) :
 - a- Conduction of air to and from the alveoli.
 - b- Regulation of the body temperature (by helping heat loss).
 - c- Control of airflow resistance (by adjusting the bronchial tone).
 - d- Providing *several protective mechanisms*. These are :
 - *Conditioning of the inspired air.*
 - *Filtration of the inspired air* from harmful foreign particles.
 - Elimination of the foreign particles by the *ciliary escalator*.
 - Formation of *immunoglobulins* (antibodies).
 - Initiation of the *sneeze and cough reflexes*.
- (2) The nasal olfactory mucosa perceives *the sensation of smell*.
- (3) The larynx is concerned with *phonation* (sound production).
- (4) The anatomical DS is the cause of the *difference between the total and effective ventilation*, and is used as *a pulmonary function test* (see next).

ASSESSMENT OF PULMONARY FUNCTIONS (THE PULMONARY FUNCTION TESTS)

The efficiency of the respiratory system can be assessed by determining one or more of the following parameters :

1. The pulmonary ventilation (see below).
2. The dead space : The presence of *non-functioning alveoli* is indicated by *a greater physiological DS than the anatomical DS* (see above).
3. The lung compliance (see next chapter).
4. The ventilation perfusion ratio (see below).
5. The static lung volumes and capacities (see above).

6. The timed vital capacity (see below).
7. The maximal breathing capacity and the breathing reserve (see below).
8. The peak expiratory flow (see below).
9. The levels of both O_2 and CO_2 in the blood (in cases of severe pulmonary insufficiency, the blood O_2 level decreases while the blood CO_2 level increases and is associated with acidosis).

PULMONARY VENTILATION (PV)

The term PV means *lung aeration with atmospheric air*, and it is tested by measuring one or both of the following volumes :

(1) The total PV or respiratory minute volume (RMV)

This is the *total volume of air that is inspired per minute*. It is calculated by multiplying the (TV) x breathing rate per minute. Since normally the former is about 500 ml, and the latter about 12 per minute, then the normal total PV (or RMV) = $500 \times 12 = 6000 \text{ ml (6 litres) per minute}$.

(2) The alveolar PV (or effective PV)

This is the *volume of air that actually ventilates the alveoli per minute*. Since about 150 ml of the inspired TV normally remain in the anatomical dead space, then *during rest only about 350 ml of the TV reach the alveoli each breath*, and the resting alveolar ventilation = $350 \times 12 = 4200 \text{ ml (4.2 litres) per minute}$.

The alveolar PV is more significant than the total PV. It is frequently altered in disease while the total PV remains constant e.g. :

1- In a case of *tachypnea* (= rapid shallow breathing due to any cause), if the breathing rate increases to 30 / minute, the TV may decrease down to 200 ml, and in this case, the total PV remains constant at 6000 ml (200×30) while the alveolar PV is markedly decreased, becoming only 1500 ml ($200 - 150 \times 30$).

2- In a case of slow deep breathing due to any cause, if the breathing rate decreases to 6 / minute, the TV may increase up to 1000 ml, and in this case, the total PV remains constant at 6000 ml (1000×6) while the alveolar PV is markedly increased, becoming 5100 ml ($1000 - 150 \times 6$).

**** Accordingly, for increasing the alveolar ventilation, patients are advised to breathe slowly and deeply.**

THE VENTILATION PERFUSION RATIO (V / P)

This is the ratio between the volume of alveolar ventilation / minute and the pulmonary blood flow / minute. Normally, the former is about 4.2 litres while the latter is about 5.5 litres (= the cardiac output of the right ventricle). Therefore, the *average normal V/P is $4.2 / 5.5 = 0.8$* . This ratio is *changed in most lung diseases* (but it may be normal in some diseases). It is also *normally higher in the apices of the lungs* (about 3.3) than in their bases (about 0.63) because of the *relatively lower pulmonary blood flow in the upper zones of the lungs due to the effect of gravity* (page 43).

THE TIMED VITAL CAPACITY (TIMED VC OR FEV₁)

The vital capacity (VC) is normally expelled in about *4 seconds*, and the *timed VC is the fraction that is expelled during the first second only* (so it is also called the *forced expiratory volume in one second or FEV₁*). It is expressed as a % of the VC (i.e. $FEV_1 / VC \%$). Normally, the FEV₁ is at least *80 % of the VC* [the normal value after 2 seconds (FEV₂) is about 94 % while that after 3 seconds (FEV₃) is 97 %].

Determination of the FEV₁ is a *good test for airway resistance*, so it is *helpful in the diagnosis and prognosis of obstructive lung diseases* in which the airway resistance is increased e.g. *asthma*. In these diseases, both the VC and FEV₁ are decreased but the latter is decreased to a much greater extent, so the ratio FEV₁ / VC is reduced. This ratio is also decreased if the lung's elasticity is reduced (e.g. in *emphysema*), but it is *usually normal in restrictive lung diseases* (page 15) because both the VC and the FEV₁ are *frequently decreased equally in these diseases* (figure 7).

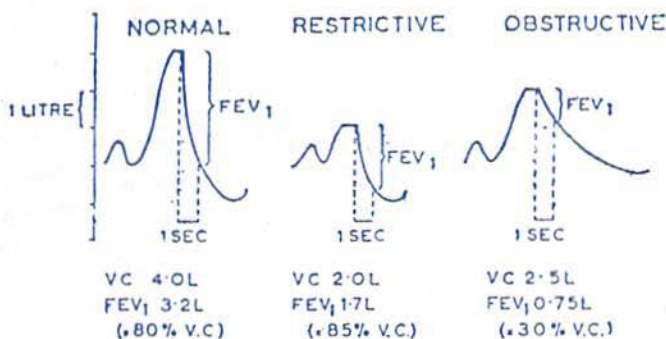


Figure 7 : Forced expiratory spiograms. Normal (left), in a case of restrictive lung disease (middle), and in a case of obstructive lung disease (right).

THE MAXIMAL BREATHING CAPACITY (MBC)

The MBC is the maximal volume of air that can be inhaled per minute by the greatest voluntary respiratory effort possible, so it is also called the *maximal voluntary ventilation (MVV)*. It is estimated by measuring the volume of expired air given out by the subject while breathing *as deep and as fast as possible in a spirometer*. Such hyperpnea is performed for only 10-15 seconds then the MBC is calculated per minute. This is because prolonged maximal breathing leads to excessive elimination of CO_2 which causes alkalosis and may be tetany.

The determination of the MBC is the best test to assess the strength of the respiratory muscles, and its average normal value is *120 (up to 170) litres per minute in young adult males*, and is less in females and in old persons. It is affected by the same factors that affect the vital capacity (page 14) but it is a *better pulmonary function test because in the early stages of certain lung diseases, the VC may be normal while the MBC is decreased*.

THE BREATHING RESERVE (BR)

The BR is the *difference between the MBC and the resting MRV*, thus if the MBC is 125 litres and the MRV is 6 litres, then the BR will be 119 litres per minute. Its measurement is a *good test for the functional reserve of the respiratory system as well as the state of physical fitness*.

THE RATIO : BR / MBC % (= THE DYSPNEIC INDEX)

The ratio : *BR / MBC % is normally higher than 90 %*, and dyspnea occurs if it drops below about 70 %, so it is also called the dyspneic index.

DYSPNEA

Dyspnea means difficulty or shortness of breathing of which the person is aware. It develops when the *dyspneic index decreases below about 70 %* (see above). This occurs due to either a decrease in the MBC or an increase in the MRV (e.g. in cases of acidosis and hyperthyroidism). Dyspnea also occurs in the following conditions :

1. *If the work of breathing increases* due to any cause.
2. *If the mechanical efficiency decreases* (e.g. in obese persons).
3. *In certain psychological conditions.*

ORTHOPNEA

This is the occurrence of *dyspnea only in the recumbent position* and is characteristic of *left sided heart failure*. In this case, both the TLC and the VC are decreased due to *pulmonary congestion*, and lying down decreases them further (due to the excess venous return and the visceral pressure on the diaphragm) which results in dyspnea.

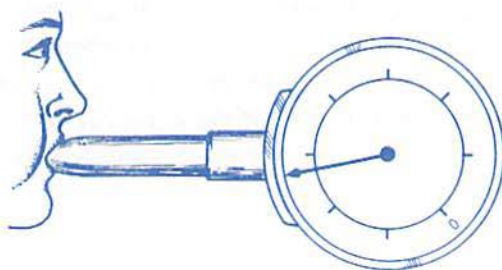


Figure 8 : The peak flow meter.

THE PEAK EXPIRATORY FLOW (PEF)

The PEF is the maximal flow rate of air during estimation of the FEV_1 . It is measured by an apparatus called the *peak flow meter* (figure 8) and its average normal value is about **8 litres / second**. It normally occurs during the first half of the FEV_1 , and similarly, it is *a good test for the airway resistance as well as the strength of the expiratory muscles*. Accordingly, it is decreased in cases of bronchial obstruction (e.g. due to asthma) and weakness of the expiratory muscles, as well as in cases of reduced elasticity of the lungs (e.g. due to emphysema).

CHAPTER 3

MECHANISM (MECHANICS) OF BREATHING

Breathing is produced by rhythmic discharge of signals from the spinal motor neurons (= anterior horn cells) that supply the respiratory muscles, which are located in the cervical and thoracic parts of the spinal cord. This discharge is controlled by 2 mechanisms :

- (1) **An involuntary automatic (subconscious) mechanism** : This is the *principal mechanism that controls respiration*, and is performed by the *respiratory centres* (see below).
- (2) **A voluntary (conscious) mechanism** : Breathing can voluntarily be stopped (e.g. during talking) or accelerated (when required). However, this can be performed for *only a short time*, and is produced by signals discharged from the *motor area of the cerebral cortex* via the cortico-spinal (= pyramidal) tract, which *directly affect the activity of the respiratory spinal motor neurons*.

Online's curse

This is an old legend that tells about a man who had *lost his automatic control of respiration*. In such case, respiration can occur only by voluntary control, and to maintain life, *he should stay awake to remember to breathe voluntarily*, which is evidently fatal due to either exhaustion or the resulting apnea if he fell asleep. Such condition can also occur if the respiratory centres are damaged e.g. in cases of bulbar poliomyelitis.

THE RESPIRATORY CENTRES

These centres *control breathing automatically*, and each consists of a collection of neurons. They are located bilaterally in the reticular formation of the *brain stem*, and include the following :

(A) MEDULLARY CENTRES

There are 2 groups of neurons in the *medulla oblongata* that indirectly control the respiratory muscles (by discharging signals downwards via special respiratory tracts to the spinal motor neurons that supply these muscles). Such neuronal groups constitute 2 centres, which are the following :

1- A dorsal respiratory group (DRG or inspiratory centre)

This consists of *I neurons* (= *Inspiratory neurons*) that cause contraction of the inspiratory muscles when stimulated, specially the diaphragm.

2- A ventral respiratory group (VRG or expiratory centre)

This consists mainly of *E neurons* (= *Expiratory neurons*) that cause contraction of the expiratory muscles when stimulated (+ some I neurons).

(B) PONTINE CENTRES

These are located *in the pons* and they control respiration by affecting *the activity of the other respiratory centres*. They include 2 centres :

1- The apneustic centre (Ap. C) in the lower part of the pons.

2- The pneumotaxic centre (Pn. C) in the upper part of the pons, forming most of the *nucleus parabrachialis* (figure 9).

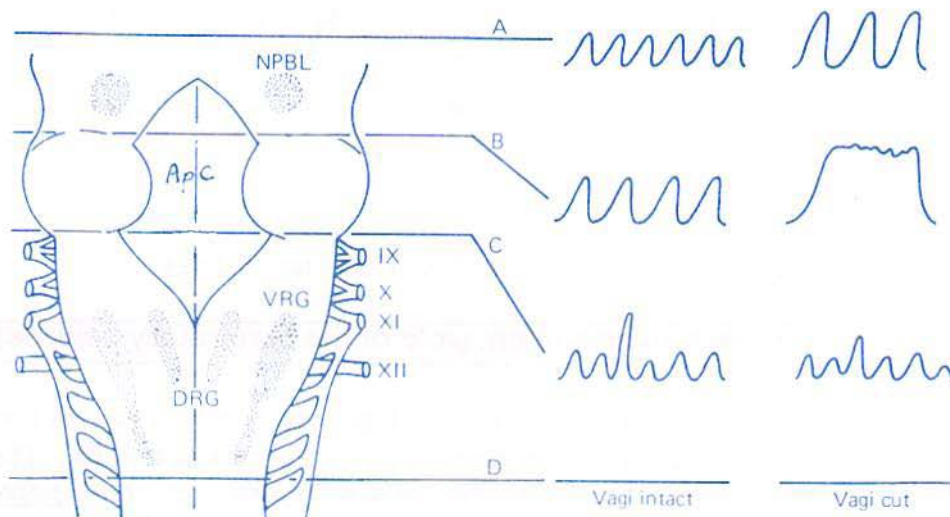


Figure 9 : The respiratory centres and effects of different transections in the brain stem with intact and cut vagi nerves. NPBL = nucleus parabrachialis (= pneumotaxic centre). AP.C = Apneustic centre, VRG and DRG = ventral and dorsal respiratory groups of neurons.

****** The respiratory neurons at both sides are inter-connected, so stimulation of either excites the respiratory muscles *at both sides of the body*. Also signals that stimulate a certain group of *medullary neurons* are associated with inhibition of the other group (see *reciprocal innervation* in the CNS).

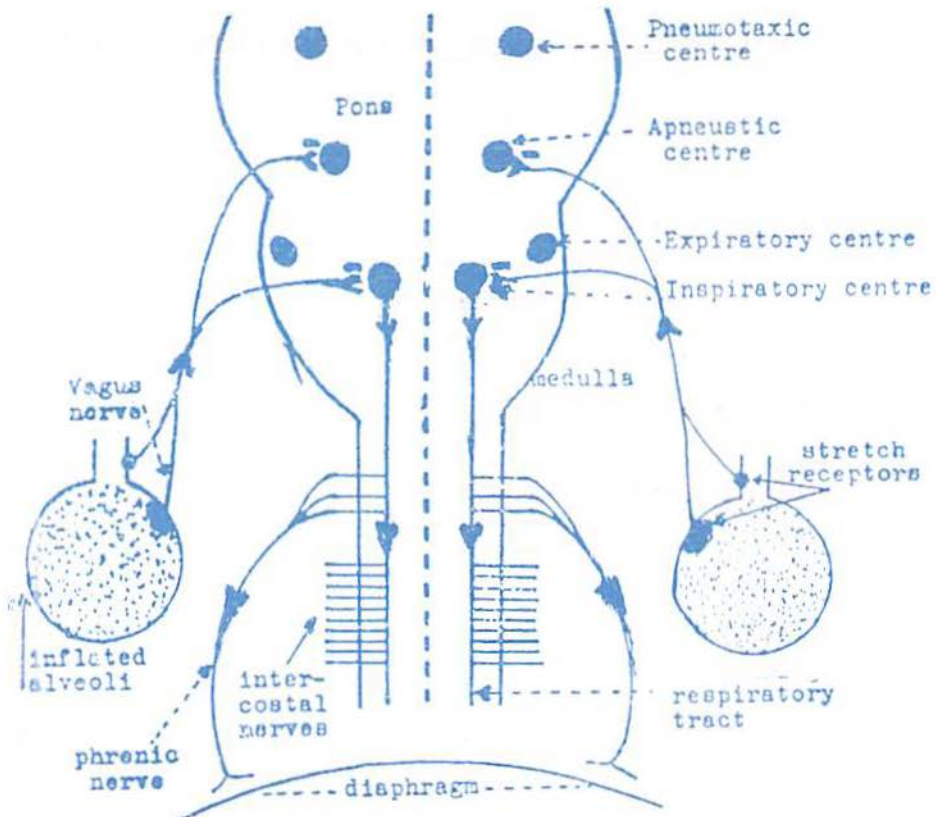


Figure 10 : Connections of the respiratory centres

Genesis of the breathing rhythm (role of the respiratory centres)

During *eupnea* (= normal resting breathing), the breathing rhythm (i.e. the alternation of inspiratory and expiratory phases) occurs as follows : The **Ap. C has an inherent tonic (=continuous) activity**, and is called the **pace-maker of respiration**. It discharges stimulatory signals to the **I neurons** in the medulla oblongata. Such discharge is **rendered rhythmic** by 2 mechanisms that **potentiate each other** :

- 1- The **Pn. C** discharges **rhythmic inhibitory signals** to the **Ap. C**.
- 2- The **afferent vagal nerve fibres** carry **inhibitory signals** to the **Ap. C** from the inflated lungs during inspiration (see **Hering-Breuer reflexes** below).

Accordingly, the medullary I neurons discharge rhythmically at a rate of **12-16 bursts per minute**, which produces rhythmic inspirations. On the other hand, the *E neurons remain quiet all the time (i.e. do not discharge)*, and *expiration follows inspiration passively* (see below).

The signals discharged from the I neurons start weakly then increase in *a crescendo manner (= ramp signals)* for about 2 seconds, after which they stop for 3 seconds (during which expiration occurs), then a new cycle starts.

MECHANISM (MECHANICS) OF INSPIRATION

Inspiration is an active process. The signals discharged from the I neurons are conducted downwards *via special respiratory tracts* to the spinal cord, where they *stimulate the spinal motor neurons that supply the inspiratory muscles*, which are located in the 3rd, 4th and 5th cervical segments as well as in all thoracic segments.

The *phrenic nerves* arise from the cervical neurons and supply the *diaphragm*, while the *intercostal nerves* arise from the thoracic segments and supply the *external intercostal muscles* (figure 10) which *extend obliquely downward and forward between the ribs*.

When the diaphragm contracts, *it moves down* leading to an increase in *the vertical diameter of the chest* (about 1.5 cm during eupnea and up to 7-10 cm during deep inspiration).

On the other hand, contraction of the external intercostal muscles leads to (a) *Elevation and eversion of the ribs (a bucket-handle movement)* (b) *Movement of the sternum forwards and its tilt upwards*. These movements *increase the anteroposterior diameter of the chest markedly* and its *lateral (or transverse) diameter to some extent*.

Accordingly, the chest cavity expands in all dimensions, leading to movement of the parietal pleura outwards. This decreases the intrapleural pressure, becoming more negative (page 32), which causes expansion of the lungs. As a result, the intrapulmonary pressure decreases from zero to about -1 mmHg (figure 11), which causes rush of about 500 ml of atmospheric air (= tidal volume) into the lungs, leading to its inflation.

The inspiratory muscles

- (1) During eupnea (normal resting breathing), the basic inspiratory muscles are the *diaphragm and external intercostal muscles* (see above).
- (2) During forced inspiration: In addition to the basic muscles, the following accessory inspiratory muscles also contract to widen the chest cavity

- 1- The sternomastoid and scaleni muscles (elevate the upper ribs).
- 2- The levator costarum and serratus posterior superior muscles (help rib elevation).
- 3- The quadratus lumborum and serratus posterior inferior muscles (prevent inward movement of the lower ribs when the diaphragm contracts).

Abdominal and costal (or thoracic) breathing

Breathing produced by contraction of the *diaphragm* is called **abdominal breathing (or respiration)** because it is accompanied by movement of the anterior abdominal wall forwards (due to rise of the intra-abdominal pressure). On the other hand, breathing by contraction of the *external intercostal muscles* is called the **costal or thoracic breathing**.

During eupnea, the abdominal breathing accounts for about 75 % of the pulmonary ventilation. However, *the diaphragm is not essential* (although it is the most important inspiratory muscle) because if its movement is compromised, **costal breathing can maintain life**. The latter also becomes equally important in deep breathing and during measurement of the vital capacity.

Effects of various lesions on respiration

1. A complete spinal cord transection *above the origin of the phrenic nerves (the 3rd cervical segment)* is fatal (e.g. in hanging) due to isolation of the respiratory centres. On the other hand, if this lesion is below the origin of the phrenic nerves (*the 5th cervical segment*), respiration is not markedly affected because the diaphragm is still functioning.
2. Bilateral phrenic nerve palsy does not affect pulmonary ventilation **at rest** (which can be maintained by costal breathing), but breathing becomes labored and the pulmonary ventilation is reduced during exercise.

MECHANISM (MECHANICS) OF EXPIRATION

During eupnea, expiration is a passive process (i.e. no muscle activity is involved). It occurs after relaxation of the inspiratory muscles by the **elastic property of the lungs and the surface tension of the fluid that lines the alveoli** (page 32), and is aided by **elevation of the diaphragm and the weight of the thoracic cage**. These effects decrease the chest volume, so the intrapleural pressure increases, becoming less -ve (page 32), which helps the lungs to recoil. As a result, the intrapulmonary pressure increases to about +1 mmHg (figure 11) leading to rush of about 500 ml of air (tidal volume).

outwards and the lungs are deflated. Such *deflation occurs slowly* because the *inspiratory muscles are partially contracted in the early expiration* (which exerts a *braking action on the lung recoil forces*).

On the other hand, *the muscles of expiration contract only* during forced expiration (e.g. during muscular exercise) and in cases of *increased airway resistance* (e.g. asthma) and *diminished elasticity of the lungs* (e.g. emphysema). The expiratory muscles include mainly the following :

1. *The anterior abdominal wall muscles* : The contraction of these muscles increases the intra-abdominal pressure, which causes bulging of the diaphragm upwards into the chest cavity, thus helping outward expulsion of the air.
2. *The internal intercostal muscles* : These muscles extend obliquely downward ~~backward~~ between the ribs, so their contraction causes depression of the ribs, which reduces the chest volume and helps expiration.

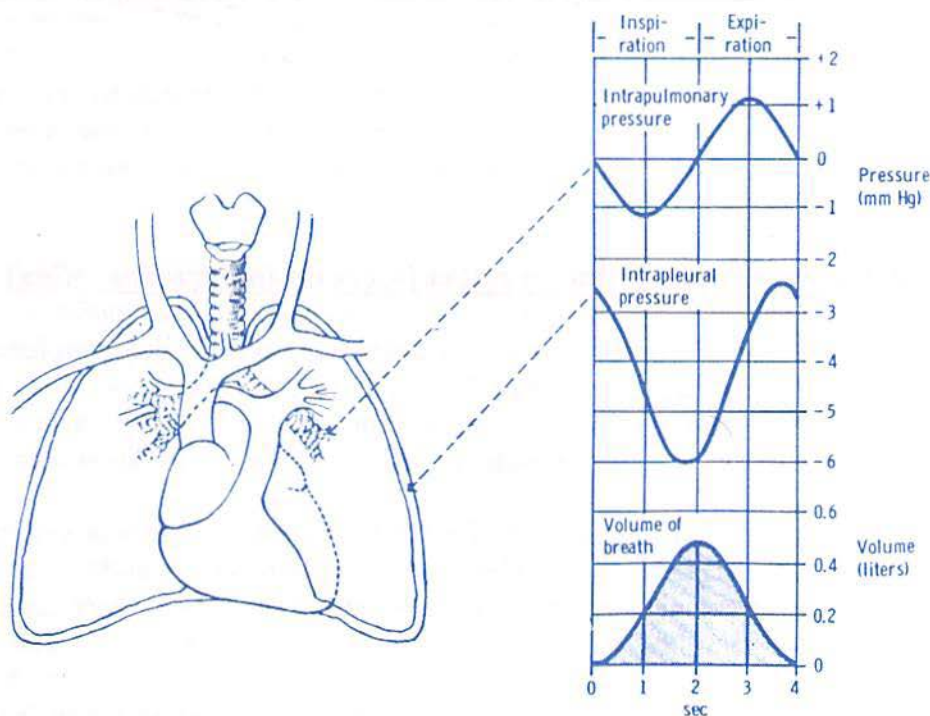


Figure 11 : Changes in the intrapleural & intrapulmonary pressures during eupnea.

Intrapulmonary (or alveolar) pressure changes during eupnea

The intrapulmonary pressure is normally zero (i.e. atmospheric) during the expiratory pause (in the midthoracic position). At the start of inspiration, it *decreases to about -1 mmHg* (figure 11) due to lung expansion. This allows rush of about 500 ml of atmospheric air into the lungs and as a result, it increases gradually till *becoming atmospheric again by the end of inspiration*.

On the other hand, at the start of expiration, it *rises to about $+1$ mmHg* due to lung recoil. This allows rush of about 500 ml of air outwards from the lungs and as a result, it decreases gradually till *becoming atmospheric again by the end of expiration*.

HERING BREUER REFLEXES

These include 2 reflexes :

1. Hering Breuer inflation reflex (= inhibito-inspiratory reflex)

Lung inflation leads to stoppage of inspiration and initiation of expiration. The receptors are *slowly-adapting stretch receptors* (= inflation receptors) located among the airway smooth muscle cells. Signals from such receptors are conducted via *afferent fibres in the vagi nerves* to the brain stem (figure 10), where they inhibit the activity of the apneustic centre (thus the inspiratory process stops and expiration starts).

2. Hering Breuer deflation reflex (= excito-inspiratory reflex)

Lung deflation leads to stoppage of expiration and initiation of inspiration. The receptors are certain *deflation receptors* which are probably a *type of irritant receptors*. Signals from such receptors are conducted via *afferent fibres in the vagi nerves* to the brain stem, where they stimulate the apneustic centre (thus the expiratory process stops and inspiration starts).

****** The inflation receptors are not adequately excited till the tidal volume exceeds 1 litre. Therefore, *the Hering Breuer reflexes normally play a little role during eupnea in adults*. However, they become important during *sleep & anaesthesia* (in which they provide a *protective mechanism against excessive inflation and deflation of the lungs*). Also, the inhibitory vagal discharge during inspiration *shares in producing rhythmic breathing* (page 26).

****** It was reported that *in newly-born infants, lung inflation excites the apneustic centre* leading to a prolonged inspiration and more lung inflation. Such response is called the *paradoxical reflex*. However, its presence is doubtful.

Effects of bilateral vagotomy on breathing

The inhibitory input to the apneustic centre (Ap.C) carried by the vagi nerves *potentiates the inhibitory input from the pneumotaxic centre (Pn.C)* and both produce rhythmic breathing (page 26). Therefore, the effects of bilateral vagotomy on breathing *depend on whether the brain stem is intact or transected, and also the level of transection* as follows (figure 9):

- (1) If the brain stem is intact or transected above the pons (A in figure 9), bilateral vagotomy renders breathing to be *deep and slow*, because the *Pn.C becomes the only source of inhibition to the Ap.C*.
- (2) If the Pn.C is isolated from the Ap.C by a mid-pontine transection (B in figure 9), bilateral vagotomy *deprives the Ap.C from all inhibitory signals*, so it discharges continuously resulting in *apneustic breathing* (see below).
- (3) If the medulla is isolated from the pons (transection C in figure 9) breathing remains *rhythmic but becomes irregular whether the vagi are intact or cut* due to *spontaneous discharge from the I neurons* (which are stimulated by a special pacemaker in the medulla called the *pre-Bottzinger complex*).
- (4) If the medulla is isolated from the spinal cord (transection D in figure 9) e.g. in hanging, *breathing stops (= apnea) and death occurs whether the vagi nerves are intact or cut* because the respiratory centres are separated from the spinal motor neurons that supply the respiratory muscles.

APNEUSTIC BREATHING (= APNEUSIS)

This is a type of breathing that occurs as a result of *bilateral vagotomy together with a midpontine transection*. It can be produced in *experimental animals but is rarely seen clinically*. It is characterized by *prolonged spasmodic inspirations interrupted by short weak expirations* (due to exhaustion of the inspiratory muscles). This occurs as a result of *continuous discharge of excitatory signals from the Ap.C to the inspiratory muscles due to its release from the inhibitory inputs of both the Pn.C and the vagi nerves*. Such pattern of breathing cannot maintain life and *leads to death due to asphyxia*.

THE INTRAPLEURAL AND INTRATHORACIC PRESSURES

The intrapleural pressure (IPP) is the pressure inside the pleural cavity. It is normally *negative* (i.e. *subatmospheric*) *during eupnea* (figure 11) and it becomes *more negative during inspiration* (see below). Such negativity is due to the *elastic properties of both the lungs and chest wall* as follows:

1. **The elastic property of the lungs** : This is due to the *elastic elements in the lungs*, the elastin & collagen fibres ($1/3$) and the *surface tension of the fluid layer that lines the alveoli* ($2/3$). It tends to decrease the lung's volume, thus *pulling the visceral pleura inwards*.
2. **The elastic property of the chest wall** This tends to expand the thoracic cage, thus *pulling the parietal pleura outwards* (page 35).

These opposing forces result in *continuous pulling of the 2 pleural layers apart from each other which creates an equal negative pressure in both the pleural & chest cavities* (so the IPP can be measured indirectly by measuring the intrathoracic pressure, commonly the *intra-esophageal pressure*).

SIGNIFICANCE (IMPORTANCE) OF THE IPP NEGATIVITY

1. It prevents collapse of the lungs and keeps them inflated.
2. It helps lung expansion during inspiration (which decreases the work of breathing)
3. It helps the venous return by the *thoracic pump* (refer to circulation).
4. It helps lymph drainage through the thoracic lymph ducts.
5. It increases the blood flow in the pulmonary vessels.

NORMAL VALUES OF THE IPP

The IPP varies with the body position as well as in the different parts of the pleural cavity due to the *effect of gravity* (see below). The following are the average normal values *in the standing position* :

1. ***In the midthoracic position*** (after a normal expiration), the IPP averages - 4 or - 5 cm H₂O (about -3 mmHg), varying from - 2.5 cm H₂O in the lung bases to -10 cm H₂O in the lung apices (figure 20 a).
2. ***During normal inspiration***, the IPP decreases to - 7.5 or - 8 cm H₂O (about -6 mmHg) due to the increase in the lung recoil forces.
3. ***During forced inspiration***, the IPP decreases to about - 40 cm H₂O, i.e. about - 30 mmHg, and is further decreased on performing the *Muller's maneuver* (= forced inspiration against a closed glottis).
4. ***During forced expiration***, the IPP increases and becomes positive at the lung bases (figure 20 b), and is further increased on performing the *Valsalva's maneuver* (= forced expiration against a closed glottis).

THE PULMONARY SURFACTANT

This is a complex mixture of several phospholipids, proteins and ions (specially Ca^{++}) that is secreted *in the alveoli* by type II alveolar cells called *the granular pneumocytes* (page 6). It is a *surface active agent* and its action is to *decrease the surface tension of the fluid film that lines the alveoli*. Such effect is *directly proportional to its concentration but inversely proportional to the surface area of the fluid* (so it is *more marked in the small alveoli*).

Factors that affect formation of the surfactant

1. **Factors that stimulate formation** : These include mainly the thyroid and glucocorticoid hormones, as well as certain proteins.
2. **Factors that inhibit formation** : These include smoking, insulin and prolonged O_2 inhalation (page 87), as well as prolonged cessation of the pulmonary circulation (e.g. during open heart surgery).

Functions of the surfactant

1. *It increases the lung compliance* (by decreasing the elastic force exerted by the surface tension), thus *helping lung expansion during inspiration*.
2. *It prevents alveolar collapse during expiration* because the alveolar surface area is decreased (so the surfactant is condensed & its action increases)
3. *It decreases the work of breathing* (by facilitating inspiration).
4. *It helps keeping the alveoli dry i.e. free from fluids* (thus it prevents easy production of pulmonary edema). This is because it decreases the suction force exerted by the alveolar fluid surface tension (such force renders the *interstitial hydrostatic pressure to be negative*, which favours fluid filtration from the pulmonary capillaries into the alveoli).
5. It plays a major role in maintaining *alveolar stability* (see below).

The respiratory distress syndrome (RDS)

This is a serious lung disease that occurs *due to deficient formation of the surfactant*. It is also called the *hyaline membrane disease*, and it may occur in adults, but it is more common in *newly born infants*, particularly :

- 1- **Premature infants** (because they are born before maturation of the surfactant-forming system). In these infants, *the lung alveoli are small* (which collapse more easily than large alveoli) and the *lungs are stiff* and contain areas of *atelectasis* (= alveolar collapse) as well as *edema*.

2- **Hypothyroid infants** (because the thyroid hormones stimulate formation of the surfactant).

3- **Infants born by diabetic mothers** (because the blood of the infant contains *excess insulin*, which inhibits surfactant formation).

****** During eupnea, intermittent deep breaths called **sighs** frequently occur. These are produced reflexly as follows: After a period of quiet breathing, the *surfactant molecules gradually sediment*, so the surface tension of the alveolar fluid tends to increase, resulting in reduction of the lung's compliance. This stimulates certain *irritant receptors* that initiate reflex deep inspiration.

ALVEOLAR STABILITY

This term means *stability of the size of different alveoli*. It is produced by 2 factors : *the surfactant and the property of alveolar interdependence*.

ROLE OF THE SURFACTANT

The surfactant maintains alveolar stability by keeping a *nearly equal pressure in various alveoli*, which occurs by **Laplace law** [= the pressure developed in the alveoli (P) equals twice the surface tension (T) divided by the radius (r) i.e. $P = 2 T / r$]. According to this law, if the (T) was the same in all alveoli, the alveoli having small (r) will have higher (P) than that in the large alveoli (which would shift air from the small to the large alveoli, resulting in collapse of the former & overdistension of the latter). However, *because the surfactant is more effective in the small alveoli* (see above), the (T) is lower in these alveoli, so the (P) in them is not increased and is maintained nearly equal to that in the large alveoli (resulting in insignificant shift of air among the various alveoli, which maintains alveolar stability).

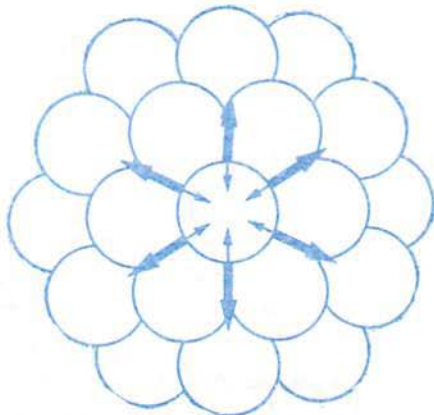


Figure 12 : The property of alveolar interdependence.

ALVEOLAR INTERDEPENDENCE

This is a property in the alveoli by which *they support each other*, so that a change in the volume of a certain group is opposed by the surrounding groups e.g. the tendency of a group of alveoli to collapse is antagonized by development of strong expanding forces in the surrounding groups (figure 12). Such property obviously helps in maintenance of alveolar stability.

THE ELASTIC PROPERTIES OF THE RESPIRATORY SYSTEM

The lungs and chest wall are *elastic structures*. Each has a resting position at which it is neither stretched nor compressed, and *they always tend to acquire this position*. The volume at the resting position is called the *relaxation volume*, and in normal adult persons, that volume of the lungs is about *one litre* while that of the thoracic cavity is about *3.5 litres*.

In the midthoracic position, each of the volume of the lungs as well as that of the thoracic cavity equals the FRC (functional residual capacity) i.e. about *2.2 litres*. This is called the *relaxation volume of the respiratory system* and at such volume, *the lungs are stretched while the thoracic cavity is compressed*. Accordingly, the lungs tend to recoil while the chest wall tends to expand, *creating the negativity of the IPP* (page 32). In other words, the *tendency of the lungs to recoil is balanced by a tendency of the chest wall to recoil by an equal degree but in the opposite direction (i.e. outwards)*.

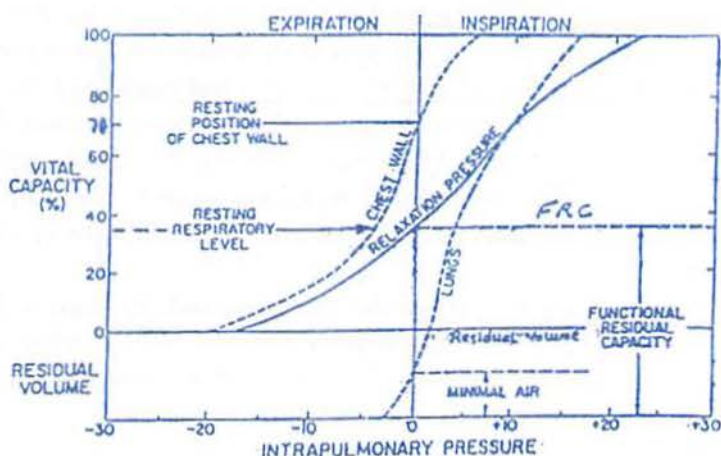


Figure 13 : The relaxation pressure curves of the whole respiratory system (the middle solid curve), the chest wall alone (the dashed left curve) and the lungs alone (the dashed right curve).

Interaction between the recoil forces of the lungs & chest wall

This is shown in the *pulmonary relaxation pressure curves* (figure 13). The relaxation pressure at a certain volume is the intrapulmonary pressure recorded at that volume while the respiratory muscles are relaxed. The relaxation pressures of either the lungs or the chest wall results from the recoil force of each, while that of the whole respiratory system is the resultant of the recoil forces of both the lungs and chest wall together (*the middle solid curve in figure 13*). The latter is constructed as follows: The subject inhales or exhales a certain volume of air from a spirometer, then the connection to the apparatus is closed and the subject relaxes his respiratory muscles as completely as possible while the intrapulmonary pressure is recorded. This procedure is repeated with other volumes, then such volumes are plotted against the corresponding intrapulmonary pressures.

The relaxation pressure curves show the following:

1. **At the midthoracic position** (when the lungs contain the FRC), the relaxation pressure of the lungs alone is about + 5 H₂O (as they tend to recoil) while that of the chest wall alone is about - 5 H₂O (as it tends to expand) and since both forces are *equal but opposite*, they cancel each other and the *relaxation pressure of the whole respiratory system becomes zero*.
2. **At volumes exceeding the FRC**, the relaxation pressure of the lungs becomes more +ve [because their recoil force increases] while that of the chest wall becomes less -ve [because its recoil force decreases as it approaches its resting volume (about 3.5 litres)] and, consequently, *the relaxation pressure of the whole respiratory system becomes positive*.
3. **At a volume of about 3.5 litres (70% of the vital capacity)**, the relaxation pressure of the lungs becomes more and more +ve [because their recoil force further increases] while that of the chest wall becomes zero [because its recoil force disappears as it reaches its resting volume] and, consequently, *the relaxation pressure of the whole respiratory system becomes more positive*.
4. **At volumes exceeding 3.5 litres**, both the lungs and the chest wall tend to *recoil inwards*, thus they operate *additively* producing a *further increase in the relaxation pressure of the whole respiratory system* (which reaches a maximum of 25-30 cm H₂O at 100 % vital capacity).
5. **At volumes less than the FRC**, the relaxation pressure of the lungs becomes less +ve [because their recoil force decreases] while that of the chest wall becomes more -ve [because its tendency to expand increases] and, consequently, *the relaxation pressure of the whole respiratory system becomes negative* (about -20 cmH₂O at the residual volume).

****** The relaxation pressure of the lungs becomes zero only at the minimal volume and it becomes negative at lower volumes (figure 13).

COMPLIANCE OF THE LUNGS AND CHEST WALL

Compliance is a *measure for the distensibility (or expansibility)* of elastic structures. It is expressed as *the increase in volume per unit increase in the distending pressure* i.e. $\Delta V / \Delta P$ (figure 14).

The compliance of the lungs alone (when removed outside the body) is normally about *0.2 litre / cmH₂O pressure* while that of the lungs and chest wall together is much less (about *0.1 litre / cmH₂O pressure*) because the lung's expansibility in the chest is limited by the rigid thoracic cage.

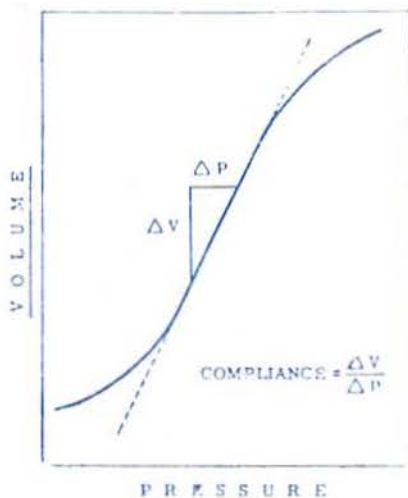


Figure 14 : Determination of the combined lung and chest wall compliance from the relaxation pressure curve (or static pressure volume curve) of the whole respiratory system (= the middle solid curve in figure 13).

Measurement of the respiratory compliance

The respiratory compliance can be measured *under static and dynamic conditions*, and the recorded values are thus called *static compliance* in the former condition and *dynamic compliance* in the latter.

- 1. Static compliance :** This is the compliance determined from the relaxation pressure curves (so these curves are also called the *static pressure volume curves*). The compliance of the lungs and thoracic wall together is obtained from the curve of the whole respiratory system (the middle

solid curve in figure 13), and is *usually measured at the steepest part of the curve*, which covers most normal resting breathing (figure 14).

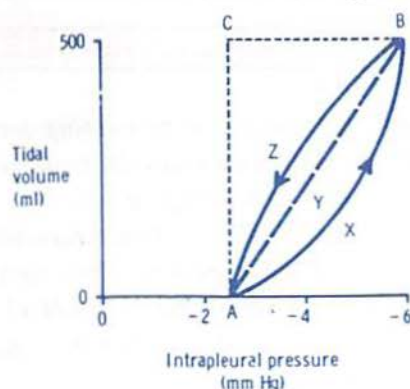


Figure 15 : The dynamic pressure volume curve during quiet inspiration (AXB) and quiet expiration (BZA). Line (AYB) represents the average lung compliance while area (AXBC) represents the work done during inspiration.

- 2. Dynamic compliance :** This is the compliance of the lungs *during the breathing cycle*, and is determined from the *dynamic pressure volume curve of the lungs* (figure 15), which is constructed as follows : The subject inhales air from a spirometer *in steps* till the maximum (50-100 ml each time) and the IPP is recorded at the end of each step (through an intra-esophageal balloon connected to a saline manometer). He then exhales in steps until the resting lung volume is resumed, and the IPP is also recorded at the end of each step. The changes in the lung volume are then plotted against changes in the IPP. The normal curve shows the following:
1. It is in the form of a *hysteresis loop* i.e. the changes in the lung volume during inflation and deflation are different (which is called *hysteresis*). It is due to *viscous properties (frictional resistance) in the lungs* (see below).
 2. The *lung compliance is greater when measured during deflation*.
 3. The *dashed line (AYB) represents the average lung compliance*.

**** The transpulmonary (or transmural) pressure = Intrapulmonary pressure – IPP.** It is the pressure that *actually affects lung inflation and deflation*. Therefore, it should be plotted against the changes in lung volume (and not the IPP). However, since the intrapulmonary pressure at the end of each inspiration or expiration is normally 0 mmHg, *the IPP will be equal to the transpulmonary pressure and thus, it can be used instead.*

**** A newly born infant normally requires a transpulmonary pressure of about + 60 mmHg at the first breath to expand his lungs.**

SPECIFIC COMPLIANCE OF THE LUNGS

The lung compliance depends on its size, thus a lung of a mouse has a smaller compliance than that of an elephant, and a patient with one lung has nearly $\frac{1}{2}$ normal compliance, and children have 2-3 times smaller compliance than adults. In addition, the compliance is greater when measured during deflation (see above). For these reasons, it is necessary to express the compliance *per unit volume*, and this is called *specific compliance*. Its determination helps in evaluating pulmonary functions, e.g. in *emphysema*, the total compliance is increased while the specific compliance is definitely reduced.

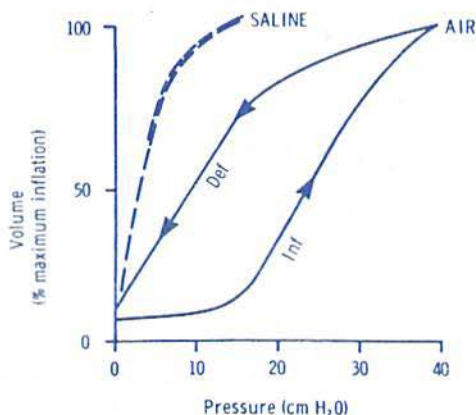


Figure 16 : Pressure-volume relations in a cat's lung outside the body when inflated and deflated, once with saline and once with air.

Factors that affect lung compliance

- 1- The size of the lung and its initial volume (see above).
- 2- The surface tension of the alveolar fluid : This decreases the compliance. Such effect is demonstrated by removing the lung of a cat outside its body and inflating & deflating it, *once with saline and once with air* while measuring the intrapulmonary pressure. **Saline decreases the surface tension to nearly zero**, and the pressure-volume curve obtained with saline shows **a higher compliance and less hysteresis**, compared with that obtained when air was used for inflation and deflation of the lung (figure 16).
- 3- **Diseases** : The compliance is decreased in the RDS (page 33) and diseases that cause lung stiffness (e.g. pulmonary fibrosis, edema & congestion). In such cases, the pressure-volume curve is **shifted downward & to the right** (figure 17). On the other hand, the curve is shifted upward & to the left in

conditions that cause *increase of the lung compliance, e.g. emphysema and old age.*

**** The thoracic compliance is decreased in cases of** (1) Deformities of the vertebral column e.g. kyphosis (= antero-posterior bending) and scoliosis (= lateral bending) (2) Arthritis of the joints of the thoracic cage or the vertebral column (3) Skeletal muscle diseases (4) Obesity.

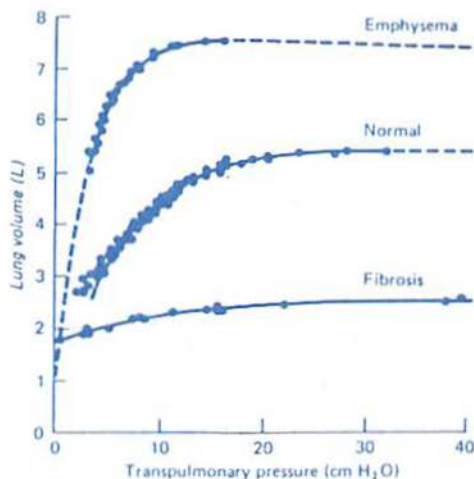


Figure 17 : Pressure volume curves in normal subjects (middle curve) and in subjects suffering emphysema (upper curve) and lung fibrosis (lower curve).

THE WORK OF BREATHING

Almost all work of breathing is performed by the *inspiratory muscles* because *expiration is normally a passive process*. It is normally **0.3–0.8 Kg-meter / minute** during eupnea, and its components include the following :

1. **Elastic (compliance) work** : This is about **65 % of the total work**, and is used for stretching the elastic tissues of the lungs and chest wall (i.e. for overcoming their elastic recoil forces).
2. **Non-elastic (resistive) work** : This is about **35 % of the total work**, and is used for resisting the frictional resistance to air movement in the lungs. It includes the following types of work :
 - a- **Airway resistance work (28 %)** : This is the work used to overcome the resistance to air flow through the respiratory passages.
 - b- **Tissue resistance work (7 %)** : This is the work used to overcome the viscous resistance in the lungs.

FACTORS THAT INCREASE THE WORK OF BREATHING

1. **Hyperpnea** : This may occur normally (e.g. during muscular exercise) or abnormally (e.g. in cases of acidosis).
2. **Reduction of the respiratory compliance** (see causes above).
3. **Deficient secretion of the surfactant** (e.g. in the RDS, page 33).
4. **Diseases that increase the resistance to air outflow** e.g. asthma and emphysema (*because the expiratory muscles also contract actively*).

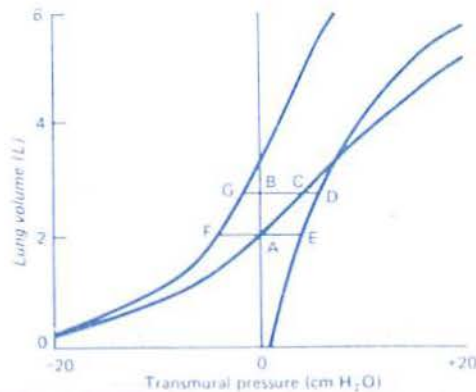


Figure 18 : Calculation of the work of breathing from the relaxation pressure curves (see text).

DETERMINATION OF THE WORK OF BREATHING

The work of breathing can be determined from one of the following curves :

- 1- **The dynamic pressure-volume curve** (figure 15) : Area *AXBCA* represents the total work done, while area *AYBCA* represents the elastic work and area *AXBYA* represents the nonelastic work (see above).
- 2- **The relaxation pressure curves** (figures 13 and 18) : Since the work is expressed in *gm.cm* (force in gram x distance in cm) and the product of *pressure x volume* is also expressed in *gm.cm* (see below), the work of breathing can be calculated by multiplying the pressure x volume. From the relaxation pressure curves, the work performed to increase the lung volume is area *ABDE*. However, the work required to inflate the whole respiratory system is area *ABC* only. This is because part of the work comes from the elastic energy stored in the thoracic cavity, and the energy lost from this cavity (area *AFGB*) equals the energy gained by the lungs (area *AEDC*).

****** The unit of pressure is gm/cm^2 , while that of the volume is cm^3 . Accordingly, the product of pressure $\times$ volume = $gm/cm^2 \times cm^3 = gm.cm$.

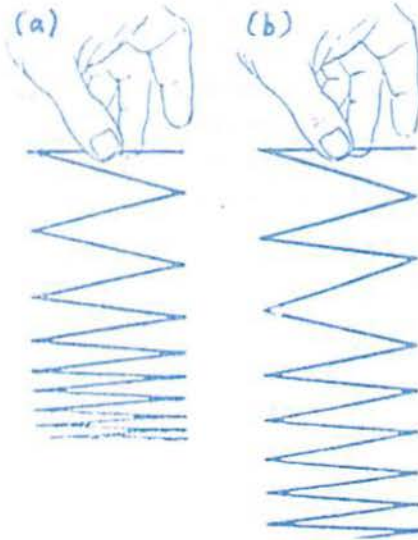


Figure 19 : A slinky spring. (a) freely suspended, (b) pulled down.

EFFECTS OF GRAVITY ON THE LUNGS

(1) EFFECT OF GRAVITY ON VENTILATION

In the upright position, the lungs are suspended in the thoracic cavity *like a slinky spring*. When such spring is freely suspended, it will be stretched mainly at its upper part, and if pulled down, its length increases mainly at its lower part (figure 19).

The lungs are similarly more expanded in their upper parts during standing. This is because the IPP is more -ve in the upper parts ($-10 \text{ cmH}_2\text{O}$) than in the lower parts ($-2.5 \text{ cmH}_2\text{O}$) *by the effect of the lung weight* (figure 20 a). Since *the expanded parts are stiffer than the non-expanded parts*, further increases in volume / unit increase in IPP are smaller in the lung apices than in the lung bases. This causes *regional differences in ventilation, which is greatest in the lung bases and becomes progressively lesser towards their apices*.

Figure 20 a shows the normal condition of the lungs during standing in the midthoracic position (i.e. when they contain the FRC and the intrapulmonary pressure is zero). The IPP is small in the base ($-2.5 \text{ cmH}_2\text{O}$), so this region has a small resting volume (thus it expands markedly during inspira-

tion because it is *situated at the steep part of the pressure volume curve*). Conversely, the IPP is high in the apex ($-10 \text{ cmH}_2\text{O}$), so this region has a large resting volume (thus it expands little during inspiration).

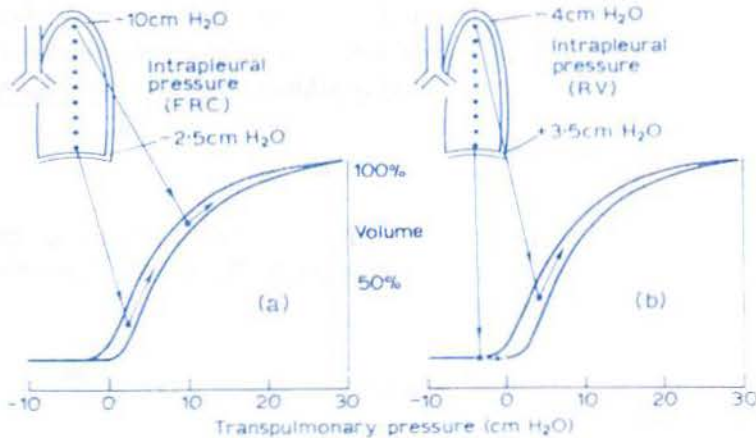


Figure 20 : Normal lung conditions *during standing* : (a) At rest when they contain the FRC. (b) After maximal expiration when they contain the RV.

It is noted that *after maximal expiration during standing*, when the lungs contain the RV, the IPP becomes $-4 \text{ cmH}_2\text{O}$ at the apices and $+3.5 \text{ cmH}_2\text{O}$ at the bases (figure 20 b). This results in 2 effects :

1- The lung bases are compressed and they are ventilated only when the IPP falls below zero. Conversely, the lung apices are located at the steep part of the pressure-volume curve, so they are better ventilated when inspiration starts. *This indicates that the distribution of ventilation is reversed at low lung volumes i.e. the lung apices are ventilated better than the lung bases.*

2- **Airway closure:** The +ve IPP at the lung bases causes collapse of the small airways in these parts (e.g. the respiratory bronchioles) and trapping of a volume of air in the alveoli. The lung volume above the RV at which the small airways at the lung bases begin to close is called the **closing volume**.

(2) EFFECT OF GRAVITY ON PULMONARY BLOOD FLOW

Due to gravity, the pulmonary blood flow at the lung apices during standing is much less than that at their bases. It is decreased in the lung apices to the extent that raises the V/P ratio to 3.3. On the other hand, the increase in blood flow at the lung bases reduces the V/P ratio there to 0.63 (page 21).

PNEUMOTHORAX

This is *entry of air inside the pleural cavity*. This may occur due to an external cause (e.g. injury of the thoracic wall) or an internal cause (e.g. rupture of the alveoli into the pleural sac). The IPP increases, leading to *collapse of the lung on the affected side and shift of the mediastinum to the normal side*. The condition is *fatal if bilateral*, and it is several types :

1. Closed pneumothorax

This is *the mildest type*, in which the hole in the pleural sac seals off and the air that entered the pleural cavity is gradually absorbed (so the collapsed lung will slowly re-expand).

2. Open (sucking) pneumothorax

In this type, the pleural cavity remains communicated to the external atmosphere, so the *IPP becomes atmospheric*. The shift of the mediastinum to the normal side increases the resistance to air flow in the intact lung and leads to kinking of the great vessels. Respiratory distress is severe and respiration is stimulated by (a) The developed hypoxia and hypercapnia (b) Activation of the deflation receptors in the collapsed lung.

3. Tension (valvular) pneumothorax

In this type, there is a flap of tissue over the hole in the pleural sac, which acts as a *flutter valve* that permits air to enter during inspiration but prevents its escape during expiration, so the *IPP rises above atmospheric*. The hypoxia is more severe, and respiration is excessively stimulated, which further increases the IPP (up to + 20 or + 30 mmHg). Kinking of the great veins causes distension of the peripheral veins and cyanosis. Shock may finally occur, which may lead to death.

Artificial pneumothorax

This is a *therapeutic procedure* that is performed to obliterate lung cavities that may form in many diseases (specially tuberculosis). Air is injected into the pleural sac in the region facing the cavity. This leads to local collapse of the lung, which obliterates the cavity and helps rapid healing. However, this procedure is rarely performed now.

CHAPTER 4

REGULATION (CONTROL) OF BREATHING

The automatic activity of the respiratory centres can be altered according to the body requirements. It generally increases with the increase in metabolic activity, specially in *muscular exercise*.

The regulation of breathing is *chemical and nonchemical (or nervous)* and both occur *reflexly* i.e. they start by stimulation of specific receptors.

CHEMICAL REGULATION OF BREATHING

This is the *main breathing regulatory mechanism*. An increase of the PCO_2 (= *hypercapnia*) or H^+ concentration (= *acidosis*) and a decrease of the PO_2 (= *hypoxia*) stimulate the respiratory centre, while opposite changes inhibit it. Such effects occur by stimulating 2 types of chemoreceptors :

1. Central (medullary) chemoreceptors

These are located at the *ventrolateral surface of the medulla oblongata* and are surrounded by brain interstitial fluid. Their only action is *to monitor the H^+ concentration in this fluid as well as that in the cerebrospinal fluid*. They are *excited by an increase in H^+ in these fluids*, in which case they discharge stimulatory signals to the respiratory centre, resulting in an increase of both the frequency and depth of breathing.

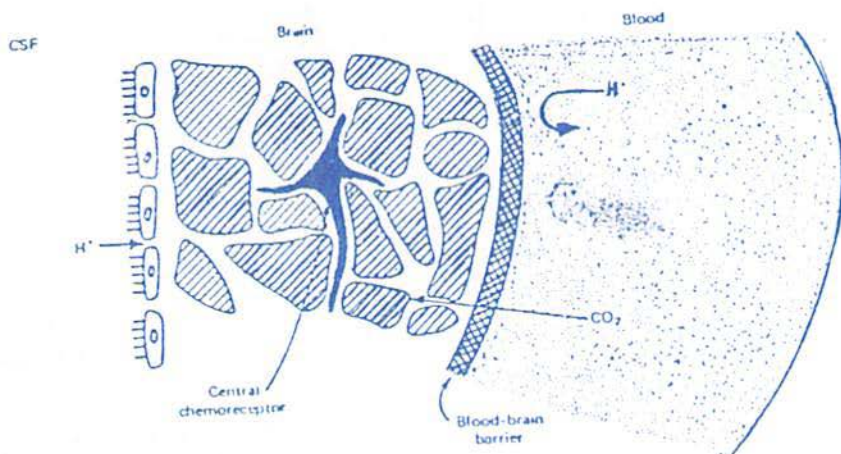


Figure 21 : A central chemoreceptor neuron. Notice that only CO_2 in the blood crosses the blood brain barrier but not H^+ .

The *only blood gas that excites the central chemoreceptors is CO_2* , so they are stimulated only in cases of *hypercapnia*. The action of CO_2 is due to the H^+ it produces in the brain fluids, which occurs as follows : The CO_2 in the arterial blood *easily crosses the blood brain barrier* (figure 21) and reaches the brain fluids, where it combines with H_2O by activity of the *carbonic anhydrase enzyme*, forming H_2CO_3 (= carbonic acid). This acid then dissociates into HCO_3^- and H^+ (which stimulates the central chemoreceptors)

****** These receptors are *insensitive to hypoxia* and cannot also detect changes in blood pH (because *H^+ cannot cross the blood brain barrier*).

2. Peripheral chemoreceptors

These receptors are present mainly in the *carotid and aortic bodies*. The former are located bilaterally at the bifurcation of the common carotid arteries while the latter are located close to the aortic arch (figure 22). The signals generated at them are conveyed to the respiratory centre by the *carotid sinus (or Hering) nerve and the aortic nerve*. These nerves are branches of the 9th and 10th cranial nerves respectively, and are commonly called the *buffer nerves* (refer to circulation).

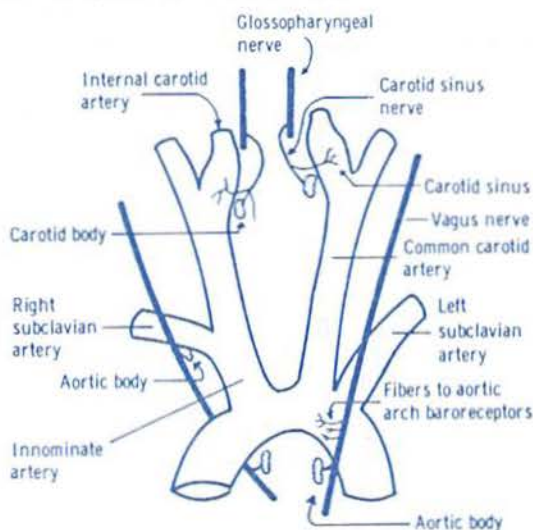


Figure 22 : The main peripheral chemoreceptors (carotid and aortic bodies).

The peripheral chemoreceptors are *most sensitive to hypoxia*, less sensitive to H^+ increase and *minimally sensitive to hypercapnia*. They are similar in size, structure and function, *but the carotid bodies are more sensitive to the gas changes, and their blood supply is also greater.*

Each carotid and aortic body is about 2 mg in weight, and consists of 2 types of cells (I and II) that are surrounded by fenestrated sinusoidal capillaries. Type II cells are probably supporting cells, while type I cells (*glomus cells*) are associated with cup-like endings of the afferent nerves, and they contain *catecholamines, specially dopamine* (which is released on exposure to hypoxia and excites the nerve endings by way of D_2 receptors).

The blood flow in the carotid bodies is very high ($0.02 \text{ ml/mg/minute}$) so the O_2 requirement of its cells is derived *mostly from the dissolved O_2* in the blood and not from oxyhaemoglobin. Accordingly, these receptors are *not stimulated in cases of anaemia and CO poisoning* because the amount of dissolved O_2 is normal in these conditions (page 80). On the other hand, they are *stimulated in the following conditions* :

- 1- When the *arterial P_{O_2} is low* e.g. in hypoxic hypoxia (see later).
- 2- When the amount of O_2 delivered to these receptors is decreased e.g. due to *reduction of the blood flow or fall of the arterial blood pressure*.
- 3- In histotoxic hypoxia caused by *cyanide poisoning*, because cyanide prevents O_2 utilization at the tissue level (see later).
- 4- By certain drugs e.g. *nicotine and lobeline, as well as by excess K^+* .

VENTILATORY RESPONSES TO CHANGES IN P_{CO_2}

CO_2 is the *normal stimulus to the respiratory centre*. It is the *normal link between the metabolic activity and pulmonary ventilation*, and it adjusts the latter *so as to keep the arterial P_{CO_2} constant at about 40 mmHg*. Thus if the arterial P_{CO_2} rises i.e. *hypercapnia* (e.g. due to increased metabolism or excess CO_2 inhalation), *breathing increases first in depth then in rate*, and this increases CO_2 excretion till the arterial P_{CO_2} falls to the normal level. On the other hand, in cases of *hypocapnia* (e.g. following prolonged hyperventilation), the respiratory centre is inhibited and breathing is decreased, and this decreases CO_2 excretion till the arterial P_{CO_2} rises to the normal level.

Most of the ventilatory response to CO_2 is produced by stimulating the *central chemoreceptors*, and only about 30 % of the response is due to stimulation of the peripheral chemoreceptors. However, the latter receptors are *stimulated first in cases of hypercapnia due to their very rich blood supply*.

Breathing (and consequently ventilation) increase proportionately with the increase in arterial P_{CO_2} (so as to keep the latter constant). However, this relation is *not unlimited*. Inhaling air containing 7 % CO_2 or more increases the arterial P_{CO_2} to the extent that depresses the respiratory centre, so breathing and ventilation are decreased and the arterial P_{CO_2} increases more. This causes severe headache, confusion, coma (= *CO_2 narcosis*) and finally death.

VENTILATORY RESPONSES TO CHANGES IN P_{O_2}

An increase in the arterial P_{O_2} (normally about 95 mmHg) i.e. *hyperoxia* slightly inhibits the respiratory centre, so decreasing both breathing and ventilation. On the other hand, a decrease in the arterial P_{O_2} i.e. *hypoxaemia* (e.g. due to O_2 lack in the atmospheric air, as occurs in high altitudes) stimulates the respiratory centre (so both breathing and ventilation are increased, leading to rise of the arterial P_{O_2} to the normal level). Such stimulation occurs *only reflexly* through stimulating the *peripheral chemoreceptors* (after damage or deafferentation of these receptors, hypoxaemia directly inhibits the respiratory centre and decreases both breathing and ventilation).

Hypoxaemia is a weaker respiratory stimulant than CO_2 excess, and is not the respiratory stimulant in the normal condition. It significantly increases breathing and ventilation *only when the arterial P_{O_2} decreases below 60 mmHg*. This is because the drop in arterial P_{O_2} leads to 2 effects that tend to inhibit the respiratory centre : (a) Decrease of CO_2 (due to the increase in ventilation). (b) Decrease of H^+ (due to the increase in reduced Hb which is a weaker acid than oxyHb).

VENTILATORY RESPONSES TO CHANGES IN BLOOD pH

A decrease in blood pH (i.e. an increase in H^+ or acidosis) stimulates the respiratory centre by stimulating the *peripheral chemoreceptors* (H^+ do not stimulate the central chemoreceptors because it cannot cross the blood brain barrier). Therefore, in severe acidosis (e.g. in diabetic ketosis), breathing is markedly increased (which is called *air hunger* or *Kussmaul's breathing*). On the other hand, an increase in blood pH (i.e. a decrease in H^+ or alkalosis) inhibits the respiratory centre (e.g. after a long period of hyperventilation).

Potentiating interaction between hypoxia and hypercapnia

Hypoxia increases the ventilatory response to hypercapnia and vice versa. (= *potentiating interaction*). Also, the presence of either increases the sensitivity of action of the other e.g. if the alveolar P_{CO_2} rises 2-3 mmHg above its normal level (40 mmHg), a slight drop of the alveolar P_{O_2} below its normal level (100 mmHg) stimulates breathing (which doesn't occur if the alveolar P_{CO_2} is normal except when the P_{O_2} drops below 60 mmHg).

Such interaction is shown in the CO_2 response curves (figure 23). The lower curve shows the relationship between the changes in alveolar P_{CO_2} and ventilation at the normal alveolar P_{O_2} (100 mmHg) while the middle & upper

curves show the same relationship when the alveolar P_{O_2} is simultaneously decreased. In the latter, it is clear that the **slope of the CO_2 response curves increases** (i.e. more ventilation occurs at a certain P_{CO_2}) and that the degree of slope is directly proportionate to the magnitude of decrease in P_{O_2} .

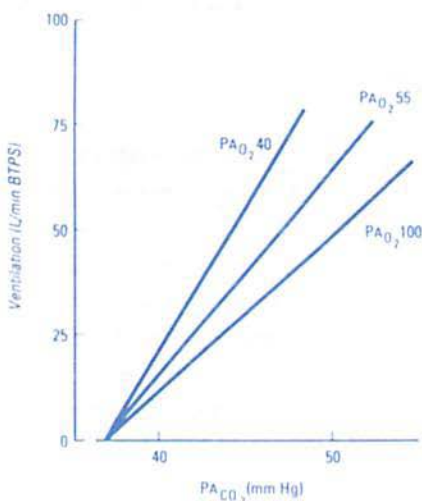


Figure 23 : The CO_2 response curves at various levels of alveolar P_{O_2} (PA_{O_2}).

****** The stimulatory effect of increased H^+ on breathing is additive to the stimulatory effects of both hypoxia and hypercapnia, particularly the latter.

NON-CHEMICAL REGULATION OF BREATHING

The respiratory centre is influenced by a wide variety of non-chemical (i.e. *nervous*) signals that produce *fine adjustments of breathing*. The origin of these signals and their effects include the following :

(1) The higher centres of the brain

(A) The cortical motor areas : Signals from these areas control voluntary breathing i.e. they can produce *voluntary hyperpnea or apnea*. However, these effects are *limited* and at a certain point called the *breaking point* they will stop. *This point is determined by the changes that occur in the arterial P_{O_2} and P_{CO_2}* e.g. during voluntary apnea, the arterial P_{CO_2} increases while the arterial P_{O_2} decreases, and both changes excite the respiratory centre, so the apnea stops. Opposite effects occur in cases of voluntary hyperpnea.

(B) **The limbic system** : This influences breathing during emotions (tachypnea occurs in some emotions while apnea occurs in some other emotions).

(C) **The hypothalamus** : This alters breathing as a part of its thermoregulatory function e.g. on exposure to heat, it causes hyperpnea in humans and panting in animals that have no sweat glands e.g. dogs (refer to metabolism).

(2) The respiratory system

(A) **From the lung's stretch (inflation) receptors** : These are the slowly-adapting receptors that initiate the *Hering-Breuer reflexes* (page 30).

(B) **From the irritant receptors** : These are rapidly-adapting, and excitation of those in the nose produces *sneezing* (or apnea if the irritant is strong e.g. ammonia), while excitation of those in the trachea or bronchi produces *coughing and bronchoconstriction*. On the other hand, excitation of those in the larynx produces *coughing and laryngeal spasm*, while excitation of those in the lungs produces *hyperpnea*.

(C) **From the juxtacapillary (J) receptors** : These are located close to the pulmonary vessels and they are stimulated by (1) Hyperinflation of the lungs

(2) Certain chemical substances e.g. serotonin

(3)

Pulmonary congestion and embolism, and their excitation in these cases initiates *the pulmonary chemoreflex* (the responses of which include apnea followed by rapid breathing, bradycardia and hypotension).

(D) **From the chest muscles and ligaments** : The mechanoreceptors in these structures discharge signals to the respiratory centre with the breathing movements that help genesis of rhythmic breathing.

(3) The cardiovascular system

(A) **From the baroreceptors** : Signals from the *arterial baroreceptors* (in the carotid sinus and aortic arch) as well as from the *atrial and ventricular baroreceptors* slightly inhibit the respiratory centre.

Adrenaline apnea : Injection of a large dose of adrenaline may cause temporary apnea due to stimulation of the arterial baroreceptors by the increased arterial B.P. (which occurs as a result of the V.C. effect of adrenaline).

Harrison's reflex : Distension of the right atrium is sometimes associated with tachypnea. Such effect was called *Harrison's reflex*, and it was described with *Bainbridge reflex*. However, like the latter reflex, it is not a constant finding and has a little physiological significance (refer to circulation).

(B) From the coronary vessels : Stimulation of certain chemoreceptors in the coronary vessels produces a reflex called *Bezold-Jarisch reflex or coronary chemoreflex*. This reflex is initiated by the _____ that initiate the pulmonary chemoreflex and also produces similar responses (see above).

(4) The skeletal muscles and joints of the limbs

The proprioceptors in these structures discharge to the nervous system leading to *hyperpnea as well as tachycardia* (refer to *Alam-Smirk reflex* in circulation). The skeletal muscles also contain chemoreceptors that are excited by metabolites (e.g. K^+ and H^+), so they are called the *metaboreceptors*, and their excitation leads to the same effects produced by the proprioceptors (so all these receptors help to increase ventilation during muscular exercise).

(5) Other sites in the body

(A) From the skin : Stimulation of the cutaneous pain and temperature receptors affect breathing by signals discharged from the hypothalamus to the respiratory centre. Mild pain produces hyperpnea while severe pain may cause apnea. Similarly, exposure to heat leads to hyperpnea while sudden exposure to cold causes apnea followed by deep inspiration.

(B) From the swallowing receptor area : This area is located at the entrance of the pharynx. Its stimulation by food during deglutition initiates inhibitory signals to the respiratory centre leading to *apnea for 2-3 seconds*. This is a protective reflex that prevents food entrance into the resp. passages. A similar effect occurs *during vomiting* when the vomitus reaches the pharynx.

HICCUP

This is a forced inspiratory act due to *spasmodic contraction of the diaphragm* during which the glottis is suddenly closed (which produces the characteristic sound of hiccup). It occurs reflexly by signals discharged in afferent vagal nerve fibres to the respiratory centre, commonly as a result of *irritation of the upper abdominal viscera*.

YAWNING

This is a respiratory act characterised by *deep inspiration and stretching of the chest wall*. It is usually associated with a desire to sleep and is an *infectious act* of unclear physiological significance. However, *like sighing* (page 34), it *helps opening of the hypoventilated alveoli and may be also the venous return to the heart*.

BREATH HOLDING (VOLUNTARY APNEA)

After a period of voluntary apnea, *the breaking point* at which breathing is resumed is affected by *psychic factors*, and *can be delayed* by either :

1. **Hyperventilating before breath holding** : This decreases the arterial CO_2 content, so it takes a long time for the arterial P_{CO_2} to increase sufficiently to stimulate the respiratory centre.
2. **Breathing 100 % O_2 before breath holding** : This increases the arterial O_2 content, so it takes a long time for the arterial P_{O_2} to decrease sufficiently to stimulate the respiratory centre.
3. **Swallowing (deglutition)** : This act prolongs the period of breath holding because it is associated with reflex inhibition of the respiratory centre.

FUNCTIONS OF THE PULMONARY VAGI NERVES

- (A) **The afferent nerves** : These transmit (a) signals of *many reflexes* e.g. the Hering-Breuer and cough reflexes (b) signals from the *chemoreceptors* in the aortic bodies, heart and lungs (c) signals from the *baroreceptors* in the aortic arch, atria and ventricles.
- (B) **The efferent nerves** : These produce (a) bronchoconstriction (b) V.D. of the pulmonary vessels (c) mucus secretion from the respiratory mucous membranes (refer to the autonomic nervous system).

EFFECT OF MUSCULAR EXERCISE ON RESPIRATION

During exercise, ventilation is markedly increased (up to 120 litres per minute or more) *to supply the O_2 requirements* of the active muscles and *eliminate the excess CO_2* , and also to allow *more heat loss*. This is produced by the following mechanisms :

1. **At the onset of exercise**, ventilation is increased by increasing *the depth of breathing*. This occurs mainly by a *nervous mechanism* (through stimulating the respiratory centre by signals discharged from both the higher centres of the brain as well as the proprioceptors & metaboreceptors in active muscles)

2. When the exercise becomes *moderate*, ventilation is further increased due to increase of *both the depth and rate of breathing*. This occurs mainly by a **chemical mechanism** (through stimulation of the respiratory centre by signals discharged from the **chemoreceptors**, which are stimulated by the changes that occur in the blood gases i.e. the rise of P_{CO_2} & H^+ and drop of P_{O_2}).

3. In severe exercises, the O_2 supply to the active muscles often becomes insufficient, resulting in **anaerobic glycolysis**. This leads to excessive formation of **lactic acid** which further stimulates the respiratory centre, resulting in more ventilation. Lactic acidosis becomes the **main respiratory stimulant** in this case because the other gas changes that stimulate respiration (the rise of P_{CO_2} and drop of P_{O_2}) are almost corrected by the resulting hyperpnea.

Other factors that may contribute in increasing breathing during exercise are (a) The raised body temperature (b) The increased venous return (through Harrison's reflex) (c) Excitation of the irritant or juxtacapillary receptors in the lungs as a result of the increased pulmonary blood flow during exercise.

****** The breathing movements can be recorded by an apparatus called the **stethograph** (figure 24).

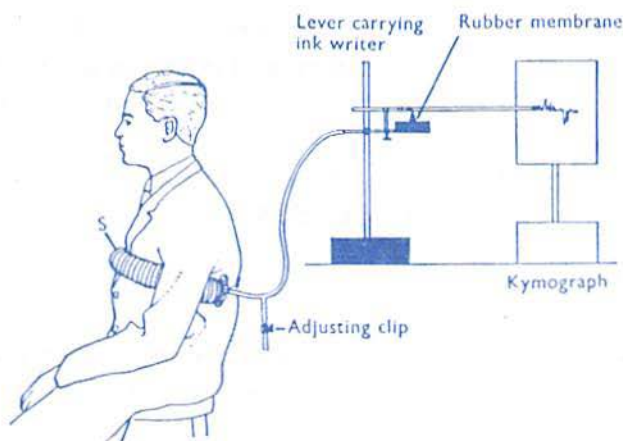


Figure 24 : Recording of the breathing movements by the stethograph (s).

CAUSES OF HYPERPNEA (RAPID BREATHING)

1. Muscular exercise (see above)
2. Certain emotions (by signals discharged from the limbic system).
3. Mild pain (by signals discharged from the hypothalamus).
4. Exposure to heat (specially in panting animals).
5. Hypotension e.g. due to *haemorrhage* (as a result of stimulation of the *peripheral chemoreceptors* by the developing hypoxia and acidosis).

6. Acidosis (increase of H^+) e.g. due to *diabetic ketosis*.
7. Hypercapnia and hypoxaemia e.g. due to *alveolo-capillary block*.
8. Asphyxia (due to rise of the arterial P_{CO_2} and drop of the arterial P_{O_2}).
9. High altitudes (due to hypoxaemia that results from lack of O_2 in the atmospheric air).
10. Pulmonary congestion and embolism (by signals discharged from the lung irritant or juxtacapillary receptors).

CAUSES OF APNEA (STOPPAGE OF BREATHING)

(A) NERVOUS CAUSES

1. Voluntary apnea (by signals discharged from the cortical motor areas).
2. Deglutition or swallowing apnea (page 51).
3. Stimulation of the baroreceptors e.g. *adrenaline apnea* (page 50).

(B) CHEMICAL CAUSES

1. Hypocapnia (e.g. after a long period of hyperventilation).
2. Severe hypoxia (by direct inhibition of the respiratory centre).
3. Depression of the respiratory centre by certain drugs (e.g. *morphine*).
4. Inhalation of 100 % O_2 during deep anaesthesia or in cases of pulmonary failure (see oxygen toxicity in chapter 8).
5. Cheyne-Stokes breathing (see below).

(C) SLEEP APNEA

Short periods of apnea often occur in *normal sleeping adults*. In most cases, this results only in *Cheyne-Stokes breathing* (see below). However, in some individuals, symptoms like morning headache, fatigue and even respiratory failure may occur (= *sleep apnea syndrome*). One of the causes of this syndrome is probably relaxation of certain tongue muscles, so it falls back and obstructs the airway (= *obstructive sleep apnea*).

Sudden Infant Death Syndrome (SIDS)

Some apparently-healthy infants may die during sleep as a result of respiratory failure. These cases are said to have SIDS. It is more common in infants of mothers who smoke and is increased by sleeping in the prone position. Its cause is unknown, but it may be a form of sleep apnea (see above).

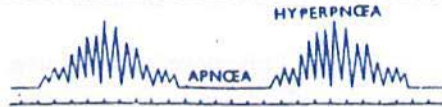


Figure 25 : Periodic breathing.

PERIODIC (CHEYNE-STOKES) BREATHING

This is a type of breathing characterized by *periods of apnea alternating with periods of hyperpnea* (figure 25). It frequently occurs after *voluntary hyperventilation for 2-3 minutes* as follows (figure 26) :

1. Hyperventilation increases the arterial P_{O_2} from 95 to 130 mmHg and decreases the arterial P_{CO_2} from 40 to 15 mmHg (= *hypocapnia*), and both effects (specially the latter) result in *apnea*.
2. During apnea, the arterial P_{CO_2} rises and the arterial P_{O_2} drops. Breathing is stimulated leading to hyperpnea. This occurs *mainly due to the resulting drop in the arterial P_{O_2}* (because the arterial P_{CO_2} is still below 35 mmHg which is insufficient to stimulate the respiratory centre).
3. The hyperpnea leads to elimination of CO_2 (i.e. *hypocapnia*) and rise of the arterial P_{O_2} , which result in apnea once again, and the cycle is repeated.

****** With each cycle, the arterial P_{CO_2} gradually increases, and after several cycles it reaches its normal level (40 mmHg), at which case normal breathing is resumed (figure 26).

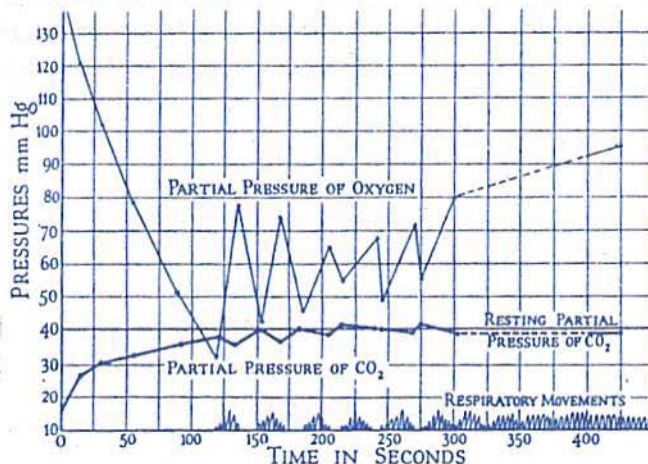


Figure 26 : Changes in the arterial P_{O_2} and P_{CO_2} during periodic breathing.

Cheyne-Stokes breathing also occurs in the following conditions :

1. **Sleep** : In some normal adult persons, apnea may occur during sleep due to *decrease in the sensitivity of the respiratory centre to CO_2* . During apnea, the arterial P_{O_2} drops while the arterial P_{CO_2} rises, and both effects stimulate

respiration resulting in hyperpnea. This increases the arterial P_{O_2} and decreases the P_{CO_2} , which result in apnea once again, and the cycle is repeated.

2. High altitudes : The O_2 lack stimulates respiration, resulting in hyperpnea. This increases the arterial P_{O_2} and decreases the arterial P_{CO_2} , resulting in apnea. During apnea, opposite changes occur in the arterial P_{O_2} and P_{CO_2} resulting in hyperpnea once again, and the cycle is repeated.

3. Some brain diseases and uraemia : In these conditions, there is abnormal *hypersensitivity of the central chemoreceptors to CO_2* . This stimulates respiration resulting in hyperpnea, which decreases the arterial P_{CO_2} . The latter leads to apnea, during which the arterial P_{CO_2} increases, resulting in hyperpnea once again, and the cycle is repeated.

4. Congestive heart failure : In this case, there is an abnormally *prolonged lung to brain circulation time*. This causes periodic breathing as follows : Heart failure is associated with hyperpnea, which *decreases the arterial P_{CO_2} in the lungs*. However, this change is detected by the respiratory centre after a delay of a few seconds (due to prolongation of the lung to brain circulation time) so hyperpnea continues for sometime then apnea occurs. During apnea *the arterial P_{CO_2} in the lungs increases*, but again this change is detected by the respiratory centre after a delay of a few seconds, so apnea continues for sometime then hyperpnea occurs once again, and the cycle is repeated.

EFFECTS OF HYPOCAPNIA

1. Apnea, which leads to periodic breathing (see above).
2. Respiratory alkalosis (refer to kidney).
3. Tetany (due to drop of the serum Ca^{++} level as a result of alkalosis).
4. V.C. of the cerebral vessels (which causes dizziness, paraesthesia, etc.).
5. An increase of the cardiac output as well as generalized V.C. (which may cause elevation of the arterial blood pressure).

The common abnormal patterns of breathing

1. Dyspnea and orthopnea (pages 22 and 23).
2. Apneustic breathing (page 31).
3. Kussmaul's breathing or air hunger (page 48).
4. Apnea, including sleep apnea (page 54).
5. Cheyne stokes breathing (page 55).

ARTIFICIAL RESPIRATION

Artificial respiration may be life saving in several conditions e.g *drowning, electrocution, CO poisoning and anaesthetic accidents*. It should always be attempted after respiration stops as long as the heart beats because it may lead to recovery of the respiratory centre.



Figure 27 : Some techniques of artificial respiration (see text).

Techniques of artificial respiration

(A) In acute respiratory failure

1. Shafer's method : The patient is placed in the *prone position*, and the rescuer (saver) puts his hands on his lower ribs and presses the sides of the chest for 2 seconds then releases the pressure for 2 seconds. This procedure is repeated *12 times per minute*, but however, it is *of little use*.

2. **Holger-Nielson's method** : This is a modification of Shafer's method, and it is *more useful but still inadequate*. The patient is placed in the *prone position* and his arms are abducted while his elbows are bent. The rescuer presses with his hands on the patient's back for 2 seconds (figure 27 A 1) then holds the patient's arms above the elbows and pulls them forward (arm lifting) for 2 seconds, which helps inspiration (figure 27 A 2), and this procedure is repeated *12 times per minute*

3. **Howard's method** : The patient is placed in the *supine position*, and the rescuer applies intermittent pressure on his chest (figure 27 B 1). However, this method is also *of little use*.

4. **Silvester's method** : This is a modification of Howard's method, and is *more useful*. The patient is placed in the *supine position*, and his arms are raised above his head (which helps inspiration) then they are lowered and the chest is pressed to help expiration (figure 27 B 2) and this procedure is repeated *12-15 times per minute*

5. **Mouth to mouth breathing** : The patient is placed in the *supine position* and his nostrils are closed by the rescuer's thumb and index fingers. The rescuer takes a deep inspiration (about twice the tidal volume) and blows into the patient's mouth, then he removes his mouth and fingers to allow passive expiration (figure 27 B 3), and this procedure is repeated *12 times per minute*. This method is the most efficient technique, although the patient receives the rescuer's expired air which contains only 15 % O₂.

(B) In chronic respiratory failure

In these cases, *mechanical respirators are required* such as the following :

1. **The resuscitator** : This apparatus supplies the patient with pulses of air or O₂ under +ve pressure through a mask that fits over his mouth and nose.

2. **The tank respirator (iron chest)** : This is an air-tight metal or plastic container inside which the patient is placed with *his head out* (figure 27 C). A leather diaphragm is automatically moved back and forth by a motor at an adjusted rate so as to create *alternating - ve and +ve pressure* inside the tank around the patient's body (to induce inspiration and expiration respectively). A *jacket model* of these respirators is now available, and modern types also contain a *built-in cough mechanism* that periodically makes the patient to cough in order to clear his lungs.

CHAPTER 5

GAS EXCHANGE IN THE LUNGS

SOME PHYSICAL LAWS OF GASES

Gas molecules are in a continuous random movement. They expand and occupy all the available volume, and also hit the wall of the container, resulting in pressure. Gases obey the following laws :

1. **BOYLE'S LAW** : "At a constant temperature, the pressure of a given quantity of gas is inversely proportional to its volume".
2. **CHARLES' LAW** : "At a constant pressure, the volume of a gas is directly proportional to the absolute temperature".
3. **DALTON'S LAW** : "In a mixture of gases, each gas exerts a pressure according to its own concentration". This is called its *partial pressure* (see below), and the total pressure of the mixture equals the sum of the partial pressures of all gases present in this mixture.
4. **HENRY'S LAW** : "The volume of a certain gas that is dissolved in a liquid is directly proportional to the partial pressure of this gas".
5. **GRAHAM'S LAW** : "The rate of diffusion of a gas is inversely proportional to the square root of its density".

The partial pressure of gases (P)

The (P) of a certain gas is the pressure exerted by this gas when present in a gas mixture, and it equals :

The percentage of this gas in the mixture x Total pressure of the gas mixture

For example, the barometric pressure at the sea level is **760 mmHg** and the composition of dry air is as follows : **20.98 % O₂, 0.04 % CO₂, 78.06 % N₂ and 0.92 % inert gases (argon, helium, neon, xenon and krypton)**. Accordingly, the (P) of these gases in dry air is as follows :

$$P_{O_2} = 20.98 / 100 \times 760 = 160 \text{ mmHg.}$$

$$P_{CO_2} = 0.04 / 100 \times 760 = 0.3 \text{ mmHg.}$$

$$P_{N_2 \text{ and inert gases}} = 78.98 / 100 \times 760 = 600 \text{ mmHg.}$$

The presence of **water vapour** decreases the percentages of other gases, and since it also exerts a (P) of **47 mmHg at the body temperature**, it also decreases the (P) of other gases e.g. in the inspired air, which is saturated with water vapour (page 17), the O₂ % is only 19.6 % (compared with 20.98 % in the dry air), and its (P) is only 149 mmHg (compared with 160 mmHg in the dry air).

STANDARDIZATION OF GAS VOLUMES

Gas and air volumes vary with both the temperature and pressure as well as with the presence or absence of water vapour. Therefore, for comparison of various volumes, the effects of these factors should be eliminated. This is achieved by prediction (correction) of the measured volume to one of the following standard conditions :

1. STPD [standard temperature and pressure, dry] i.e. 0°C, 760 mmHg, dry.
2. BTPS [body temperature and pressure, saturated with water vapour].
3. ATPS [ambient temperature and pressure, saturated with water vapour].

GAS DISSOLUTION IN FLUIDS

Gases dissolved in fluids are referred to as gases in *physical solution*, and they exert a *partial pressure (P) or tension*. The concentration of a gas that is dissolved in a fluid depends on 2 main factors :

1. The (P) of the gas : The greater the (P) of the gas in the fluid, the more the amount of the gas that will be dissolved in the fluid.
2. The solubility of the gas : The greater the solubility of the gas in the fluid the more the amount of the gas that will be dissolved in the fluid.

GAS DIFFUSION THROUGH MEMBRANES

Gases diffuse from regions of high partial pressures to regions of lower partial pressures, and their rate of diffusion through membranes depends on the following factors :

1. The pressure gradient : The greater the difference between the gas pressures at the 2 sides of the membrane, the more will be the rate of gas diffusion
2. The molecular weight of the gas : The rate of gas diffusion is inversely proportional to the square root of the molecular weight of the gas.
3. The solubility of the gas : The rate of gas diffusion is directly proportional to the solubility of the gas in the membrane.
4. The nature of the membrane : The rate of gas diffusion is directly proportional to the surface area of the membrane and inversely proportional to its thickness.

FICK'S LAW OF GAS DIFFUSION

This law correlates the various factors that determine the volume of a gas that diffuses across a given membrane per unit time as follows (*figure 28*) :

Volume of gas diffusion $\propto \frac{A \cdot D \cdot (P_1 - P_2)}{T}$. Where,

A = Surface area of the membrane.

T = Thickness of the membrane.

P₁ and P₂ = Partial pressures of the gas at the 2 sides of the membrane.

D = solubility / $\sqrt{\text{molecular weight}}$. It is a *constant* that is directly propor-

tional to the gas solubility and inversely proportional to the square root of its molecular weight.

****** It is noticed that the volume of gas diffusion is *directly proportional to* (a) The surface area of the membrane (b) The solubility of the gas in the membrane (c) The difference between the gas pressures at the 2 sides of the membrane, while it is *inversely proportional to* (a) The thickness of the membrane (b) The molecular weight of the gas.

THE ALVEOLO-CAPILLARY (OR RESPIRATORY) MEMBRANE

The alveolo-capillary membrane is a *blood-air barrier* because it separates the air in the alveoli from the blood in the pulmonary capillaries. Its average surface area is **70 square meters**, and its thickness is only **0.2 – 0.6 micron** although it consists of several layers, which include the following :

1. The capillary endothelial cells.
2. The capillary basement membrane.
3. A thin interstitial space between the capillary and alveolar epithelium.
4. The alveolar basement membrane.
5. The alveolar epithelial cells.
6. A thin layer of fluid that lines the alveoli.

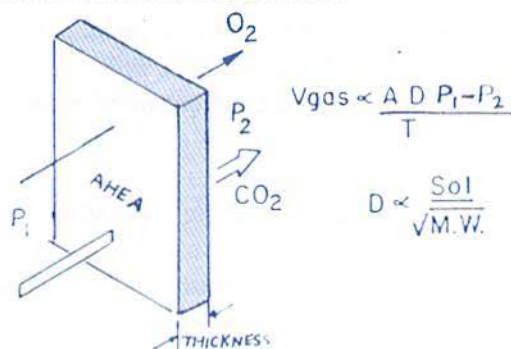


Figure 28 : Factors that affect gas diffusion through the alveolo-capillary membrane. Notice the greater diffusion of CO₂ compared with O₂ diffusion.

GAS EXCHANGE ACROSS THE ALVEOLO-CAPILLARY MEMBRANE

This occurs by *simple diffusion*, and is affected by the factors explained in *Fick's law* (see above). The alveolo-capillary membrane favours O_2 and CO_2 exchange because (a) Its surface area is large (b) It is very thin (c) It is freely permeable to these gases (these gases are fat-soluble, so they dissolve easily in the membrane cells, which facilitates their transport).

ARTERIALIZATION OF THE VENOUS BLOOD IN THE LUNGS

This process occurs as follows : The average P_{O_2} In the *venous blood* flowing to the lungs (through the *pulmonary arteries*) is 40 mmHg, while it is about 100 mmHg in the alveolar air. Therefore, O_2 diffuses from the alveolar air to the venous blood. On the other hand, the average P_{CO_2} In the *venous blood* is 46 mmHg, while it is about 40 mmHg in the alveolar air. Therefore, CO_2 diffuses from the venous blood to the alveolar air. *After equilibration, the (P) of these gases in the pulmonary veins (which carry arterial blood) become nearly equal to their corresponding values in the alveolar air (the P_{O_2} about 97 mmHg and the P_{CO_2} about 40 mmHg).*

EQUILIBRATION OF THE RESPIRATORY GASES IN THE LUNGS

The molecular weight of O_2 is smaller than that of CO_2 (32 and 44 respectively), thus the diffusion rate of O_2 *would be more rapid*. However, since the *solubility coefficient of CO_2 is normally much higher than that of O_2 (see below), the diffusion rate of CO_2 is normally about 20 times more than that of O_2 .*

Due to this fact, equilibration of CO_2 in the lungs is completed in only *0.010 - 0.015 second* while that of O_2 requires *0.2- 0.3 second* although CO_2 diffuses down a pressure gradient of only 6 mmHg (from 46 to 40 mm Hg) while O_2 diffuses down a pressure gradient of 60 mmHg (from 100 to 40 mmHg) as explained above.

****** Because blood normally travels along a pulmonary capillary in about 0.75 second during rest, and about 0.25 second during severe exercise, it follows that it is *almost completely oxygenated in both conditions*.

****** The *solubility coefficient of a ceretain gas* is defined as the volume of that gas that dissolves in one ml of liquid. At the normal body temperature, it is about *0.022 ml for O_2 and 0.511 for CO_2 .*

****** In the diseases associated with thickening of the respiratory membrane i.e. cause alveolo-capillary block (e.g. diffuse interstitial pulmonary fibrosis), *O₂ diffusion is reduced much earlier than CO₂ diffusion*. This is because the lung diffusion capacity for O₂ is much smaller than that for CO₂ (see above). In these diseases, severe hypoxia may occur without significant CO₂ retention in the body.

THE DIFFUSION CAPACITY OF THE LUNG

Diffusion capacity for a gas

The diffusion capacity of the lung for a certain gas is “*the volume of this gas that diffuses across the alveolo-capillary membrane in ml / minute / mmHg of pressure gradient*”.

Normal values

The normal lung diffusion capacity for O₂ *during rest* is 20-25 ml / minute / mmHg, while that for CO₂ is about 20 times greater (400-500 ml / minute / mmHg) because of the much greater solubility of the latter (see above). During exercise, these values increase 2-3 times due to *a marked increase in the surface area of the alveolo-capillary membrane*, which occurs as a result of the following :

1. An increase in the alveolar surface area (by opening the inactive alveoli).
2. An increase in the number of active pulmonary capillaries.
3. Dilatation of the pulmonary capillaries.

Measurement

It is difficult to measure the lung diffusion capacity for either O₂ or CO₂. However, measurement of the *diffusion capacity for carbon monoxide (CO)* is much easier. The normal value of the latter is nearly equal to that of O₂ (about 25 ml / minute / mmHg), and its determination is used as an index for the efficiency of gas diffusion in the lungs.

CHAPTER 6

OXYGEN TRANSPORT (CARRIAGE) BY THE BLOOD

According to the level of P_{O_2} , *oxygen flows downhill* from the alveolar air to the blood then into the tissues (figure 29). Oxygen supply to the tissues is the function of the *respiratory and cardiovascular systems*, and the amount delivered depends on (a) The amount of O_2 that enters the lungs (b) The efficiency of gas exchange in the lungs (c) The capacity of the blood to carry O_2 (d) The rate of blood flow to the tissues.

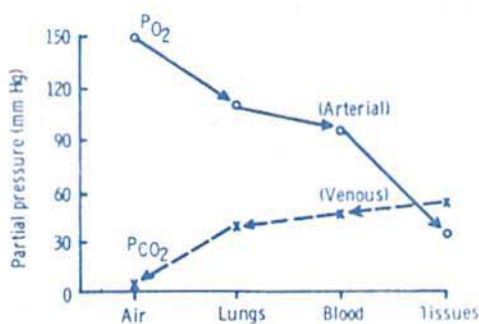


Figure 29 : Directions of O_2 and CO_2 diffusion in the body.

OXYGEN IN THE BLOOD

Oxygen is present in the blood in the following 2 forms :

(1) In physical solution (i.e. dissolved in the plasma and blood cells)

This is normally *a very small amount* (see table in page 65) but it is important because (a) It determines the P_{O_2} in the blood, which in turn determines the direction and rate of flow of O_2 as well as the degree of saturation of haemoglobin with O_2 (b) It is the only stimulant to the peripheral chemoreceptors (page 47).

(2) In chemical combination with haemoglobin (Hb)

This constitutes *the majority of the blood O_2 content* (see table in page 65), so it is essential for supplying adequate amounts of O_2 to the tissues both during rest and exercise. *Hb increases the O_2 carrying capacity of the blood about 70 times.* O_2 combines loosely to Hb, and is also easily dissociated from it, and these processes occur *very rapidly* (in less than 0.01 second). The Hb molecule contains *4 ferrous atoms*, each of which can reversibly bind to one O_2 molecule *without changing the ferrous state*, so this binding is a form of oxygenation and not oxidation.

Chapter 6**Oxygen transport (carriage) by the blood**

Therefore, each Hb molecule can bind 4 O₂ molecules. The saturation of Hb with O₂ occurs gradually in 4 steps as follows :



When fully saturated, each gram of Hb carries about 1.34 ml of oxygen

The following table shows the normal (P), % Hb saturation with O₂ and volumes of O₂ & CO₂ in ml / dL (100 ml) in arterial & venous blood at rest.

	O ₂ volume (ml / dL)		CO ₂ volume (ml /dL)	
	<u>dissolved</u>	<u>combined</u>	<u>dissolved</u>	<u>combined</u>
Arterial blood : P _{O₂} 95 mmHg, P _{CO₂} 40 mmHg and Hb saturation with O ₂ 97 %	0.3	19.5	2.6	46.4
Venous blood : P _{O₂} 40 mmHg, P _{CO₂} 46 mmHg and Hb saturation with O ₂ 75 %	0.1	15.1	3	49.7

Notice that normally at rest, the arterial blood contains about 19.8 ml O₂ / dL while the venous blood contains only 15.2 ml O₂ / dL, which indicates that each 100 ml of arterial blood supplies the tissues with 4.6 ml O₂.

OXYGEN CONTENT

This is the volume of O₂ (in ml) present in *chemical combination* (i.e. bound to Hb) in 100 ml blood.

OXYGEN CAPACITY

This is the maximal volume of O₂ (in ml) that can be carried in chemical combination by 100 ml blood (i.e. when Hb is completely saturated with oxygen).

OXYGEN % SATURATION

This is the % saturation of Hb with O₂, and it is calculated as follows

$$\text{O}_2 \text{ \% saturation} = \frac{\text{oxygen content}}{\text{oxygen capacity}} \times 100$$

COEFFICIENT OF OXYGEN UTILIZATION

This is the % of O_2 in the arterial blood that is taken by the tissues, and it is calculated as follows :

$$\text{Coefficient of } O_2 \text{ utilization} = \frac{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}{\text{arterial } O_2 \text{ content}} \times 100$$

****** The average normal values for the P_{O_2} and O_2 content in the arterial and venous blood *during rest* are shown in the above table (page 65).

****** Since there is normally about 15 gm Hb / ml blood and each gm combines with about 1.34 ml O_2 , then the normal O_2 capacity of blood =

$$15 \times 1.34 = 20 \text{ ml } O_2 / 100 \text{ ml blood (approximately)}$$

$$\text{The coefficient of } O_2 \text{ utilization at rest} = \frac{19.5 - 15.1}{19.5} \times 100 = \text{about } 25 \%$$

During exercise, this coefficient increases to **75 % or more**. It is to be noted that the venous blood always contains an amount of O_2 (even in the most severe exercises), so it is commonly called mixed venous blood.

THE PHYSIOLOGIC SHUNTS

These are normal shunts that allow drainage of some systemic venous blood into the pulmonary venous blood (which is arterial blood after equilibration with the alveolar air). This systemic venous blood is derived from :

1. The bronchial veins, which drain some of their blood into the pulmonary capillaries and veins.
2. The coronary veins, which drain some of their blood directly into the left side of the heart via the *thebesian veins* (refer to circulation).

As a result of these physiologic shunts, the P_{O_2} and % saturation of Hb with O_2 in the systemic arterial blood (about 95 mmHg and 97 % respectively) are *normally slightly less* than their corresponding values in the blood that has equilibrated with alveolar air at the venous ends of the pulmonary capillaries (about 97 mmHg and 97.5 % respectively).

THE O_2 Hb DISSOCIATION CURVE

This curve shows the relation between the O_2 pressure and the % saturation of Hb with O_2 . It is **constructed** by placing small volumes of blood in several *tonometers* (special glass containers), and exposing each tonometer to a particular O_2 pressure at 37 °C. Enough time is allowed for equilibration

then the blood is analyzed to determine its O_2 content. The % saturation of Hb with O_2 is calculated and then plotted against the O_2 pressure. The curve is normally *sigmoid in shape i.e. S-shaped* (figure 30 A).

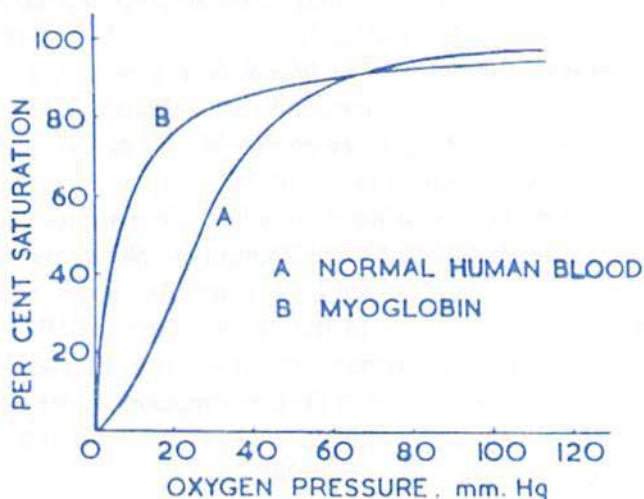


Figure 30 : The O_2 dissociation curve for blood Hb (A) and myoglobin (B).

Cause of the sigmoid shape of the O_2 Hb dissociation curve

The Hb molecule is formed of **4 haem units**, so it is called **Hb₄** (page 65). Each unit is an iron-containing porphyrin that consists of one ferrous atom attached to 4 pyrrole rings, and *can combine with one oxygen molecule (O_2)*.

This combination occurs *in steps*, and when a unit is oxygenated, the affinity of the other units to O_2 increases. This is because oxygenation of the haem units changes the shape of the Hb molecule from the *Tense or T state* (= state of less affinity to O_2) to the *Relaxed or R state* (= state of increased affinity to O_2). The facilitation of binding of O_2 to Hb as a result of previous O_2 binding is known as the *cooperative effect of O_2* , and this is the *cause of the sigmoid shape of the O_2 – Hb dissociation curve*.

Physiological significance of the O_2 Hb dissociation curve

1. At O_2 pressure of 100 mmHg, Hb is almost 100 % saturated with O_2 . This indicates that at the normal arterial P_{O_2} (about 95 mmHg), Hb is nearly fully saturated with O_2 (about 97 %) which helps adequate supply of O_2 to the tissues.

2. At O_2 pressure of 70 mmHg, Hb is about 93 % saturated with O_2 . This indicates that the alveolar or arterial P_{O_2} can be lowered by about 1/3 without much decrease in the % saturation of Hb with O_2 (as occurs in high altitudes and the pulmonary diseases that cause alveolo-capillary block).

3. At O_2 pressure of 40 mmHg, Hb is about 75 % saturated with O_2 . This is the *O_2 pressure in the venous blood during rest*, and the O_2 content in this blood is about 15.2 ml % (see table in page 65). This indicates that the *tissues extract 4.6 ml of O_2 from each 100 ml blood*. Since about 5.5 litres of blood perfuse the tissues each minute at rest (= the cardiac output), they will obtain *250 ml O_2 per minute*, which is adequate for their needs.

4. At O_2 pressures between 40 and 20 mmHg, *the curve becomes steep* meaning that the slightest decrease in O_2 pressure results in marked desaturation of Hb (i.e. marked decrease in the % saturation of Hb with O_2). This effect is useful in *muscular exercise* in which the arterial P_{O_2} decreases below 40 mmHg due to the increased O_2 consumption by the active muscles, resulting in more desaturation of Hb (i.e. more O_2 is unloaded or dissociated from Hb and delivered to the active muscles).

5. At lower O_2 pressures than 20 mmHg, O_2 dissociation from Hb is insignificant and consequently, the released amount of O_2 to the tissues becomes minimal. In this case, the tissues require an additional source of O_2 , and this is supplied by the *myoglobin* present in the muscles (see below).

****** If the curve is analyzed in the opposite direction (i.e. from left to right), it will show *the phases of O_2 binding to Hb at various O_2 pressures*, and in this case, it may be called the *O_2 association curve* !!.

MYOGLOBIN

This is a red oxygen-carrying pigment found in skeletal muscles, specially those specialized for prolonged contraction (i.e. the slow muscles that are rich in red fibres). Its molecular weight is $\frac{1}{4}$ that of Hb (16700), and its molecule contains *only one haem unit that contains one ferrous atom and can bind only one oxygen molecule (O_2)*.

The myoglobin O_2 dissociation curve lies to the left of the Hb O_2 dissociation curve and is in the form of *rectangular hyperbola* (figure 30B). This indicates that myoglobin retains (or stores) O_2 when the O_2 pressure is high and releases it only at low O_2 pressures. It performs a *complementary function to blood Hb* because the steep part of its curve comes after that of the Hb curve (thus at low O_2 pressures, myoglobin can release its O_2 content to the tissues at a time the release of O_2 from the blood Hb becomes minimal).

**FACTORS THAT AFFECT (SHIFT) THE O₂ HB DISSOCIATION CURVE
(= FACTORS THAT AFFECT THE AFFINITY OF HB FOR O₂)**

The O₂ Hb dissociation curve may be shifted to the right or to the left. When the curve is shifted to the right, the % saturation of Hb with O₂ is decreased at any given O₂ pressure, indicating decreased affinity of Hb for O₂ (i.e. more O₂ dissociation from Hb & a greater delivery of O₂ to the tissues). On the other hand, shift of the curve to the left produces opposite effects.

The P₅₀

This is the O₂ pressure at which Hb is 50 % saturated with O₂. It is an index for shifts of the O₂-Hb dissociation curve. **The normal P₅₀ at rest is about 26 mmHg.** It increases when the curve is shifted to the right (i.e. when the Hb-O₂ affinity is decreased) while it is decreased when the curve is shifted to the left (i.e. when the Hb-O₂ affinity is increased).

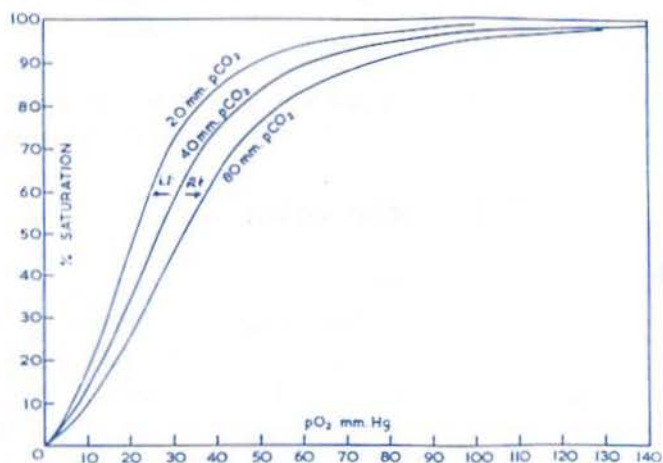


Figure 31 : Effects of changes in the arterial P_{CO₂} on the O₂-Hb diss. curve.

FACTORS THAT SHIFT THE CURVE TO THE RIGHT

These factors convert the Hb molecule *from the R form to the T form* (i.e. from the state of more affinity to O₂ to the state of less affinity to O₂) resulting in more O₂ dissociation from Hb and its delivery to the tissues (see above). The most important of these factors include the following :

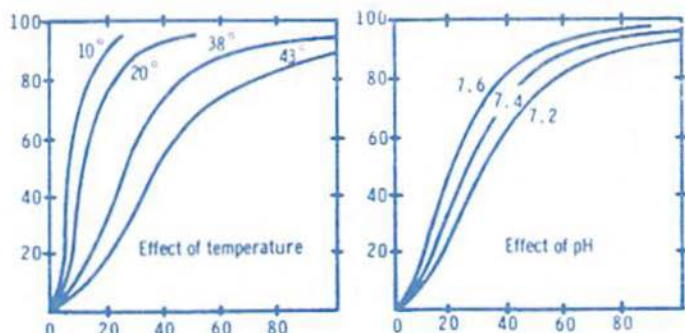


Figure 32 : Effects of changes in the temperature (left) and blood pH (right) on the O₂-Hb dissociation curve.

1. An increase in H⁺ concentration (i.e. drop of the blood pH or acidosis). This effect is called **Bohr's effect** (figure 32).
2. An increase in the arterial P_{CO₂} (figure 31). This shifts the curve to the right secondary to lowering of the blood pH (so it is also a **Bohr's effect**).
3. An increase in the body temperature (figure 32).
4. An **increase in the 2,3 DPG** inside the red blood cells (see below).
5. An increase in Hb concentration (e.g in pregnancy and polycythaemia).

**** The first 4 factors act during muscular exercise**, helping more O₂ dissociation from Hb and greater delivery of O₂ to the active muscles.

Role of 2-3 DPG in O₂-Hb dissociation

2-3 DPG (2-3 diphosphoglycerate) is formed as a product of *glycolysis* in the red blood cells. It combines with beta polypeptide chains of Hb A and converts Hb to the T form, which favours release of O₂ from Hb as follows :



Accordingly, when the 2-3 DPG increases, the affinity of Hb to O₂ decreases and the curve is shifted to the right. On the other hand, if its concentration decreases, the affinity of Hb to O₂ increases and the curve is shifted to the left (see below).

Factors that increase 2-3 DPG synthesis

1. Alkalosis e.g. at high altitudes (see below).
2. Muscular exercise.
3. Anaemia and other causes of hypoxia (e.g chronic lung diseases).
4. Some hormones (e.g. thyroxine, the growth hormone and androgens).

****** The increase in 2-3 DPG at high altitudes antagonizes the effect of the developed alkalosis to shift the O_2 -Hb dissociation curve to the left, and shifts the curve to the right (which increases O_2 delivery to the tissues).

Factors that decrease 2-3 DPG synthesis

1. Blood storage for long periods (see below).
2. Acidosis [however, during exercise, 2-3 DPG increases in spite of the tendency to acidosis, probably as a result of the temporary hypoxia that occurs in the active muscles due to the increased O_2 consumption].

FACTORS THAT SHIFT THE CURVE TO THE LEFT

These factors convert the Hb molecule *from the T form to the R form* (i.e. from the state of less affinity to O_2 to the state of more affinity to O_2) resulting in less O_2 dissociation from Hb and less delivery of O_2 to the tissues (see above). The most important of these factors include the following :

1. A decrease in H^+ concentration (i.e. rise of the blood pH or alkalosis).
2. A decrease in the arterial P_{CO_2} (figure 31).
3. A decrease in the body temperature (figure 32).
4. A **decrease in the 2,3 DPG** inside the red blood cells. This commonly occurs in *stored blood for long periods* (see above).
5. A decrease in Hb concentration e.g. in anaemia (see below).
6. **Carbon monoxide poisoning** (page 80).
7. **Fetal blood** (see below).

****** *Hb must be kept inside the red blood cells to be concentrated.* In cases of haemolysis, it escapes into the plasma where it is diluted, resulting in shift of the O_2 -Hb dissociation curve to the left. This is a *serious condition because Hb will be unable to release its O_2 content (although it is fully saturated with O_2) except at very low O_2 pressures.*

****** Fetal blood contains Hb F (fetal Hb), the molecule of which contains a *pair of alpha polypeptide chains and a pair of gamma polypeptide chains* (instead of the alpha and beta polypeptide chains present in Hb A, refer to blood). *2-3 DPG does not bind to Hb F* because 2-3 DPG can combine *only with the beta polypeptide chains of Hb A* (see above), which are lacking in Hb F. For this reason, the *affinity of Hb F to O_2 is high*, which results in (a) Shift of the O_2 -Hb dissociation curve to the left (b) Facilitation of transfer of O_2 from the mother to the fetus (in whom O_2 dissociation from Hb is favoured by the relatively low P_{O_2} at the fetal tissues).

CHAPTER 7

CO₂ TRANSPORT (CARRIAGE) BY THE BLOOD

Depending on the P_{CO_2} level, CO_2 flows downhill from the tissues to the blood, then to the lung alveoli, where it is eliminated outwards (figure 29).

CO₂ IN THE ARTERIAL BLOOD

The arterial blood normally contains about **49 ml CO₂ /dL** (100 ml) which are present in the following forms (see the table in page 65) :

1. In physical solution (dissolved in the plasma and RBCs)

This is *free CO₂* and it constitutes only about 5 % of the total CO₂ content in the arterial blood (about **2.6 ml %**). However, it is important since it *determines the arterial P_{CO₂}* (normally about **40 mmHg**).

2. In reversible chemical combination

This constitutes about 95 % of the total CO₂ content in the arterial blood (about **46.4 ml %**), and is present in the following 2 forms :

a- Bicarbonate (HCO₃⁻) : This is present as *KHCO₃ in the red blood cells and NaHCO₃ in the plasma*, and it constitutes about 90 % of the total CO₂ content in the arterial blood (about **43.8 ml %**).

b- Carbamino compounds : These constitute 5 % of the total CO₂ content in the arterial blood (about **2.6 ml %**) and are formed by combination of CO₂ to the amino groups of the amino acids in the proteins (forming *R.NHCOOH*, where R is the protein). *Some CO₂ combines to the plasma proteins, but the majority combines to Hb forming Hb.NHCOOH (carbHb)*.

Importance of the high arterial CO₂ content

CO₂ forms an *important buffer system (HCO₃⁻ / H₂CO₃)* that antagonizes changes in the blood pH. In the arterial plasma, the ratio HCO_3^- / H_2CO_3 is normally **20 / 1**, and *the arterial blood pH is kept constant at 7.4 as long as this ratio is not changed* (refer to kidney).

THE TIDAL CO₂

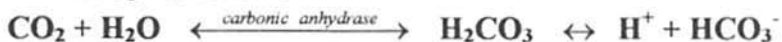
This is the volume of CO₂ that is added to each 100 ml of arterial blood during its flow through the tissues. It is normally about **3.7 ml during rest**, and it increases the CO₂ content in the venous blood to **52.7 ml / dL** and the P_{CO_2} to about **46 mmHg** (see table in page 65). It is transported in the same

proportions as the CO₂ already present in the arterial blood (i.e. **mostly in the chemical form**) so as to keep the ratio $\text{HCO}_3^- / \text{H}_2\text{CO}_3$ unchanged and the blood pH constant at 7.4. Accordingly, it is transported as follows :

1. 10 % (0.4 ml) remain in the **physically dissolved form** equally in the plasma and the red blood cells (5 % each).
2. 90 % (3.3 ml) is transported in 2 **chemically-combinated forms** :
 - a- 25 % (0.8 ml) as **carbamino compounds**, mostly **carbHb**. Binding of CO₂ to the proteins is rapid and requires no enzymes or other catalysts and the **reduced Hb forms more carbHb than oxyHb**.
 - b- 65 % (2.5 ml) as **bicarbonate ions (HCO₃⁻)** , in both the red blood cells (60 %) as well as the plasma (5 %).

Mechanism of formation of HCO₃⁻ (role of carbonic anhydrase)

HCO₃⁻ is formed by **hydration of CO₂ to H₂CO₃** then dissociation of the latter into H⁺ and HCO₃⁻ as follows :



The hydration reaction is accelerated by the **carbonic anhydrase enzyme** which is **present only in the red blood cells** (figure 33). For this reason, 60% of HCO₃⁻ is formed in the red cells and only 5 % in the plasma (see above).

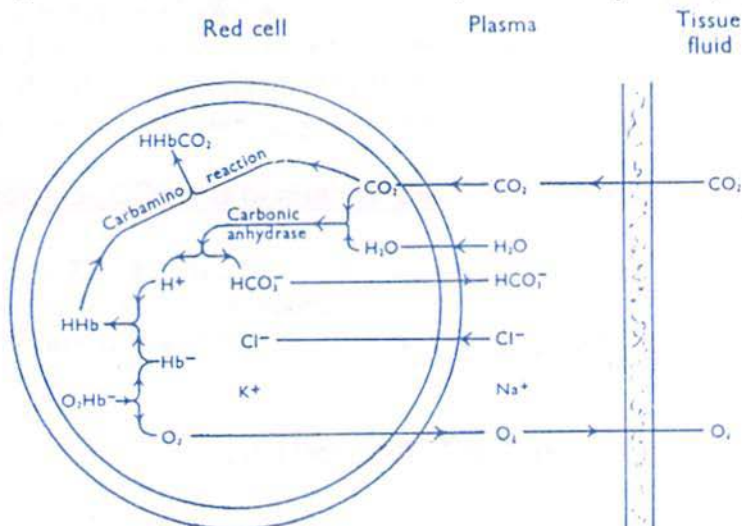


Figure 33 : Buffering of CO₂ in the red blood cells. Notice the Cl⁻ shift.

Fate of HCO₃⁻ in the plasma and red blood cells

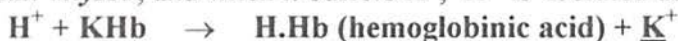
The formed HCO₃⁻ in the plasma combines with Na⁺, forming NaHCO₃. Inside the red blood cells, about 30 % of the formed HCO₃⁻ combine with K⁺ (see next), forming KHCO₃ while 70 % diffuse into the plasma and combine with Na⁺ forming NaHCO₃. To maintain electric neutrality, other -ve ions diffuse from the plasma into the red blood cells and combine with K⁺. These are mostly Cl⁻ (figure 33) so the process is called **chloride shift** (see below).

Sources of K⁺ inside the red blood cells

Both oxyHb (HbO₂) and reduced Hb (Hb) are *weak acids* because their *isoelectric points are less than the pH inside the red blood cells*, which is 7.3 (refer to blood). Accordingly, they combine with K⁺ (the main base present inside the red cells), forming KHbO₂ and KHb. However, *HbO₂ is more acidic*, so it combines with more K⁺. Therefore, in the tissues when HbO₂ delivers O₂ and becomes reduced Hb, some K⁺ is released as follows :
KHbO₂ (K-oxyhemoglobinate) → KHb (K-hemoglobinate) + O₂ + some K⁺
Some K⁺ is also liberated as a result of H⁺ buffering (see next).

Buffering (fate) of H⁺ in the plasma and red blood cells

The released H⁺ after dissociation of H₂CO₃ is *buffered in the plasma by the plasma proteins and in the red blood cells by Hb. Reduced Hb is a stronger H⁺ acceptor than oxyHb*, and when it buffers H⁺, K⁺ is liberated as follows



H.Hb is a very weak acid that minimally disturbs the pH (see below).

Role of the plasma and red blood cells in tidal CO₂ carriage

- 1. Role of the plasma:** This carries about 10 % of the tidal CO₂ (5 % dissolved and 5 % as HCO₃⁻, and a very small amount as carbamino compounds).
- 2. Role of the red blood cells:** These carry about 90 % of the tidal CO₂ (5 % dissolved, 25 % as carbHb and 60 % as HCO₃⁻).

Consequences of addition of the tidal CO₂

1. The dissolved amount of CO₂ increases, so the P_{CO₂} in the venous blood increases to **46 mmHg**
2. The carbamino compounds are increased (specially carbHb).

3. HCO_3^- increases in both the red blood cells and the plasma.
4. Cl^- increases in the red blood cells and decreases in the plasma.
5. The tonicity inside the red blood cells increases due to the increase in both HCO_3^- and Cl^- . This withdraws water from the plasma by *osmosis* (= **water shift**). Consequently, the *volume of the red blood cells and the haematocrit value increase slightly in the venous blood* (see below).
6. The formed H^+ is efficiently buffered, so the blood pH drops only slightly (from 7.4 in the arterial blood to 7.36 in the venous blood).

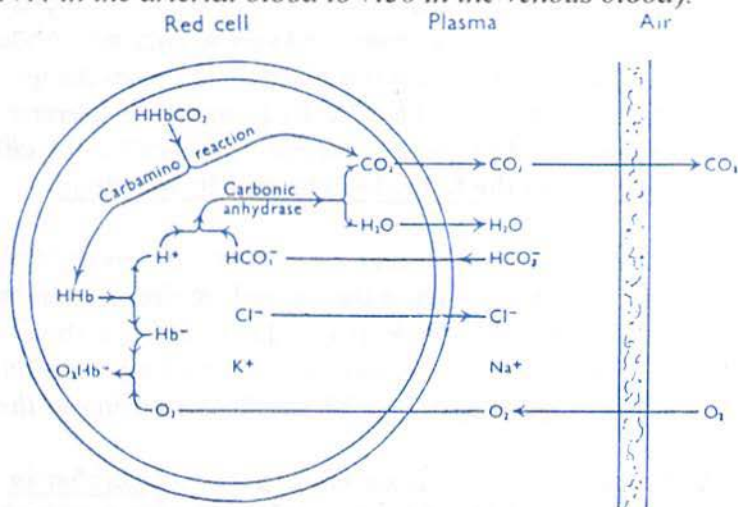


Figure 34 : Tidal CO_2 excretion in the lungs. Notice reversal of the Cl^- shift.

TIDAL CO_2 EXCRETION IN THE LUNGS

When the venous blood reaches the lungs in the pulmonary artery (in which the P_{CO_2} is 46 mmHg), it is exposed to the alveolar air in which the P_{CO_2} is lower (40 mmHg). Accordingly, the excess physically dissolved CO_2 diffuses passively from the venous blood to the alveolar air under a **pressure gradient of 6 mmHg**. The excess CO_2 in the carbamino compounds is also dissociated and excreted in the alveolar air.

Also H^+ is released from H.Hb (see below) and binds to HCO_3^- that is obtained from KHCO_3 , forming H_2CO_3 . The **carbonic anhydrase enzyme** then catalyzes dissociation of H_2CO_3 into water and CO_2 , which is excreted in the alveolar air. As a result, the HCO_3^- concentration in the red blood cells decreases, so HCO_3^- diffuse from the plasma into the red blood cells while Cl^- diffuse from the red blood cells to the plasma to maintain electric neutrality, and this is sometimes called **reversal of the chloride shift** (figure 34).

****** H^+ is released from H.Hb due to O_2 diffusion from the alveoli and formation of HbO_2 , which is a **weaker H^+ acceptor than reduced Hb** (page 74). HbO_2 then combines with the released K^+ from KHCO_3 and forms KHbO_2 .

****** About 200 ml CO₂ are normally excreted / minute during rest because each 100 ml blood supply 3.7 ml CO₂, and the pulmonary blood flow (= cardiac output of the right ventricle) is about 5.5 litres / minute.

THE CHLORIDE SHIFT

This is a phenomenon that occurs *while blood flows at the tissues*. The tidal CO₂ diffuses inside the red blood cells where it is mostly converted into HCO₃⁻ by activity of the *carbonic anhydrase enzyme*. About 70 % of HCO₃⁻ then diffuse outwards into the plasma, and in exchange, Cl⁻ diffuse from the plasma into the red blood cells *to maintain electric neutrality*. This process is completed in about 1 second, and is called the *chloride shift* (figure 33). **It results in the following changes in the blood :**

1. The HCO₃⁻ concentration increases in both the red cells and the plasma.
2. The Cl⁻ concentration increases in the red cells & decreases in the plasma
3. The tonicity inside the red cells increases due to accumulation of both Cl⁻ and HCO₃⁻. This leads to water movement from the plasma into the red cells by *osmosis* (= water shift), which results in *swelling of the red cells*.

****** The haematocrit value is normally about 3 % higher in the venous blood than in the arterial blood because of (a) The increase in the red cell volume as a result of *water shift* (b) The return of some tissue fluid to the circulation via the *lymph vessels* (which concentrates the venous blood)..

****** Reversal of the chloride shift occurs in the lungs (page 75).

GAS EXCHANGE IN THE TISSUES AND LUNGS

(1) IN THE TISSUES

The P_{CO₂} in the tissues is higher than that in the arterial blood (about 46 and 40 mmHg at rest respectively). Therefore, CO₂ diffuses passively down this gradient from the tissues to the blood, in which it is carried in the plasma and red blood cells as described above and *chloride shift occurs*.

On the other hand, the P_{O₂} in the arterial blood is higher than that in the tissues (about 95 and 40 mmHg at rest respectively). Therefore, O₂ diffuses passively down this gradient from the arterial blood to the tissues, and oxyHb is changed into reduced Hb.

(2) IN THE LUNGS

The P_{CO_2} in the venous blood is more than that in the alveolar air (about 46 and 40 mmHg at rest respectively). Therefore, CO_2 diffuses passively down this gradient from the venous blood to the alveolar air (to be eliminated in the expired air) and *the chloride shift is reversed* (figure 34).

On the other hand, the P_{O_2} in the alveolar air is higher than that in the venous blood (about 100 and 40 mmHg at rest respectively). Therefore, O_2 diffuses passively down this gradient from the alveolar air to the blood and combines with Hb, forming oxyHb.

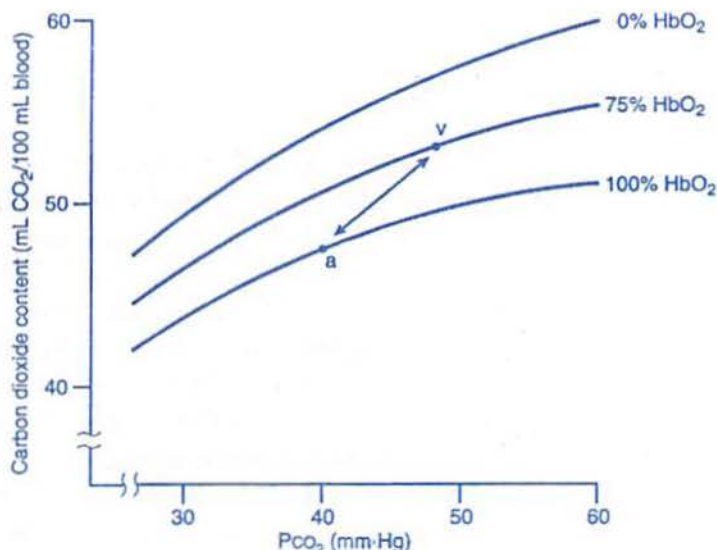


Figure 35 : The CO_2 dissociation curves.

THE CO_2 DISSOCIATION CURVES

These curves show the relation between the P_{CO_2} level in the blood and the total CO_2 content /dL. They are more *linear than the O_2 -Hb dissociation curve* and are *constructed in a similar way* (page 66). 3 curves are usually drawn (figure 35), *one for the arterial blood during rest* (in which Hb is about 97 % saturated with O_2), and *one for the venous blood during rest* (in which Hb is about 75 % saturated with O_2), and a *third one for completely reduced (i.e. deoxygenated) blood* (in which Hb is zero % saturated with O_2).

SIGNIFICANCE OF THE CO₂ DISSOCIATION CURVES

1. Study of the physiological CO₂ dissociation curve

Point (A) represents the CO₂ conditions in the *arterial blood at rest* (where the P_{CO₂} is 40 mmHg and the CO₂ content 49 ml / dL) while point (V) represents the CO₂ conditions in the *venous blood at rest* (where the P_{CO₂} is 46 mmHg and the CO₂ content 52.7 ml / dL).

The line that joins points (A) and (V) is the *physiological CO₂ dissociation curve*. It represents the changes in P_{CO₂} and CO₂ content that occur in the systemic blood as it flows from the arteries to the veins during rest, and from its extension upwards, the changes that would occur when the CO₂ production increases can be predicted.

2. Study of the Haldane's effect

Haldane's effect is the *effect of O₂ on the CO₂-carrying ability of Hb*. The presence of the curve of the arterial blood normally below that of the venous blood indicates that at any P_{CO₂}, the venous (deoxygenated) blood carries more CO₂ than does the arterial (oxygenated) blood. This is true since *reduced Hb carries more CO₂ than oxyHb as carbHb* (page 73).

Such effect is *physiologically significant* because deoxygenation of oxyHb in the tissues will help carriage of more tidal CO₂ as carbHb, while oxygenation of reduced Hb in the lungs will help CO₂ release from Hb and its excretion in the alveolar air then elimination in the expired air.

For this reason, *if oxyHb is not deoxygenated in the tissues, the addition of the tidal CO₂ would increase the P_{CO₂} to 54 mmHg instead of 46 mmHg* (as shown from the line extending from point V on meeting the curve of the arterial blood). In this case, there is less formation of carbHb (due to the low affinity of oxyHb to CO₂) and *more physical dissolution of CO₂* in the blood (which increases the P_{CO₂}). The later results in *acidosis*, which is favoured because *oxyHb is also a weak H⁺ acceptor* (page 74).

****** The exposure of blood to the high P_{CO₂} in the tissues shifts the O₂-Hb dissociation curve to the right (= **Bohr's effect**, page 70) i.e. facilitates Hb-O₂ unloading, and this helps Hb-CO₂ loading (= **Haldane's effect**). Conversely, the exposure of blood to the low P_{CO₂} in the lungs shifts the O₂-Hb dissociation curve to the left i.e. facilitates Hb-O₂ loading, and this helps Hb-CO₂ unloading. Therefore, the loading and unloading of both O₂ and CO₂ are *mutually-helpful (i.e. help each other) in both the lungs and tissues*.

CHAPTER 8

HYPOXIA, ACCLIMATIZATION AND CYANOSIS

DEFINITION AND TYPES OF HYPOXIA

Hypoxia is O_2 deficiency at the tissue level. It is a better term than anoxia (= complete O_2 lack at the tissues) because the latter never occurs clinically. On the other hand, hypoxaemia refers to O_2 deficiency in the blood. Depending on the cause, hypoxia is classified into 4 main types :

- | | |
|----------------------|------------------------|
| 1. Hypoxic hypoxia. | 2. Anaemic hypoxia. |
| 3. Stagnant hypoxia. | 4. Histotoxic hypoxia. |

(1) HYPOXIC HYPOXIA

In this type, the *hypoxia occurs secondary to hypoxaemia*. The P_{O_2} and O_2 content as well as the % saturation of Hb with O_2 are all decreased in both the arterial and venous blood (see table in page 81). There is also cyanosis due to presence of excessive amounts of reduced Hb in the blood (page 85). The common causes of hypoxic hypoxia include the following :

1. Breathing air that contains low O_2 % than normal (e.g. in high altitudes).
2. Inadequate pulmonary ventilation (*respiratory pump failure*) : This results from *defective breathing* which may occur due to either :
 - a- Depression of the respiratory centre (e.g. in morphine poisoning).
 - b- Weakness or paralysis of the respiratory muscles (e.g. in poliomyelitis).
 - c- Fatigue of the respiratory muscles (e.g. in bronchial asthma).
 - d- Pneumothorax, hydrothorax, chest deformities and emphysema.
 - e- Shallow rapid breathing (e.g. in pulmonary congestion or embolism).
3. *Gas exchange failure*: This occurs in diseases that cause *alveolo-capillary block* (e.g. diffuse pulmonary fibrosis and pulmonary edema) or *ventilation perfusion imbalance*.
4. *Right to left cardiac shunts* (e.g. *atrial and ventricular septal defects*) : These transfer venous blood to the left side of the heart (without oxygenation in the lungs), resulting in hypoxaemia and consequently hypoxia.

(2) ANAEMIC HYPOXIA

In this type, the hypoxia occurs due to *deficiency of the amount of Hb available to carry O_2* . In the arterial blood, the O_2 content is decreased but the P_{O_2} is normal, while both are decreased in the venous blood (see table in

page 81). Its **common causes include the following** :

1. *All types of anaemia.*
2. Transformation of Hb by certain toxins and drugs into compounds that are *unable to carry O₂* e.g. **sulph-Hb and methHb** (refer to blood).
3. *Carbon monoxide (CO) poisoning* (see next).

Carbon monoxide (CO) poisoning

CO combines with Hb and forms **carboxy-Hb (COHb)**. The affinity of Hb to CO is about **210 times its affinity to O₂**, and **COHb cannot bind to O₂** (because CO binds to the ferrous atoms in the Hb molecule). CO also **shifts the O₂-Hb dissociation curve to the left** (page 71) and this further decreases delivery of oxygen to the tissues, resulting in severe hypoxia (which is fatal if 70 – 80 % of Hb is converted to COHb).

Symptoms

1. Symptoms of other types of hypoxia (*see below*) specially **headache and nausea** (however, since the arterial P_{O2} is normal, the peripheral chemoreceptors are not stimulated, so **respiration is little stimulated**, page 47).
2. The skin and mucous membranes are **cherry red** (colour of COHb).
3. Symptoms of **brain damage** (mental changes & parkinsonism like state).

Treatment

1. Removing the patient away from the source of the gas, keeping him at complete rest and improving his ventilation by **artificial respiration**
2. Breathing a mixture of **95 % O₂ and 5 % CO₂**. O₂ helps COHb dissociation, while CO₂ stimulates respiration. **Hyperbaric O₂** (= O₂ under high pressure) can also be used (see below).
3. **Exchange blood transfusion** may be required in severe cases.

(3) STAGNANT (ISCHAEMIC) HYPOXIA

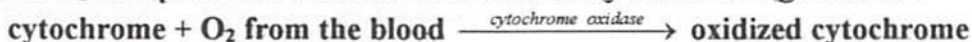
In this type, the hypoxia occurs due to blood stagnation (or slow circulation) in the tissues. Both the **P_{O2} and O₂ content are normal in the arterial blood but decreased in the venous blood** (see table in page 81), leading to **cyanosis** in the affected areas. Blood stagnation may be either :

1. **Generalized** (i.e. allover the body) e.g. in congestive heart failure, circulatory shock, and polycythaemia vera (refer to blood).
2. **Localized** e.g. in areas of venous thrombosis or V.C. (the latter is characteristic of **Raynaud's disease**, in which severe V.C. occurs in the tips of the fingers and toes, specially on exposure to cold).

(4) HISTOTOXIC HYPOXIA

In this type, the hypoxia occurs due to **blockage of the enzymes** involved in tissue (or internal) respiration (= the process of gas exchange in the cells). Thus, although the arterial P_{O_2} and O_2 content are normal, yet O_2 cannot be extracted, and consequently, **their levels are increased in the venous blood** and approach their levels in the arterial blood (see table below).

Tissue respiration depends on a haem-like substance called **cytochrome** and certain enzymes, specially **cytochrome oxidase**. These are concerned with O_2 transport from the blood to the tissues by the following reaction :



The oxidized cytochrome releases its O_2 to the tissues and becomes reduced. The reduced cytochrome then gets O_2 from the blood and becomes oxidized, and the cycle is repeated. The **commonest cause of histotoxic hypoxia is cyanide poisoning** (see next).

Cyanide poisoning

The cyanide salts **block the cytochrome oxidase enzyme**, so the cells become hypoxic because they become unable to extract O_2 from the blood. The condition can be improved by **hyperbaric oxygenation** and also by giving **methylene blue or nitrite salts** (these substances convert Hb into metHb, which reacts with cyanide and form the non-toxic compound **cyan-metHb**).

The following table shows the P_{O_2} and O_2 content in the arterial and venous blood in various types of hypoxia :

	<u>ARTERIAL BLOOD</u>		<u>VENOUS BLOOD</u>	
	P_{O_2}	O_2 content	P_{O_2}	O_2 content
HYPOXIC HYPOXIA	decreased	decreased	decreased	decreased
ANAEMIC HYPOXIA	normal	decreased	decreased	decreased
STAGNANT HYPOXIA	normal	normal	decreased	decreased
HISTOTOXIC HYPOXIA	normal	normal	increased	increased

SYMPTOMS OF HYPOXIA

Sudden severe hypoxia is fatal due to deprerssion of the respiratory centre. On the other hand, mild and moderate hypoxia lead to the following :

1. **Nervous symptoms** e.g. headache, fatigue, disorientation and drowsiness.
2. **Digestive symptoms** e.g. anorexia (loss of appetite), nausea and vomiting.

3. *Respiratory symptoms* (tachypnea and may be periodic breathing).
4. *Cardiovascular symptoms* : Tachycardia, high cardiac output and hypertension, followed by fainting in long-standing cases. In chronic hypoxia, the alveolar hypoxia causes *pulmonary V.C.*, which may lead to pulmonary hypertension and overstraining of the right ventricle.

ACCLIMATIZATION

This term refers to the **adaptive mechanisms that occur in high altitudes** (i.e. on prolonged exposure to low O_2 pressures). At high altitudes, the *composition of air remains constant but its total pressure falls*. This results in *marked reduction of the P_{O_2} in atmospheric air*.

The minimal alveolar P_{O_2} that can be tolerated without loss of consciousness is **40 mmHg** (at which Hb is about 75 % saturated with O_2). The altitude at which this occurs *varies* : If the subject was *breathing air*, this P_{O_2} is reached when the atmospheric pressure decreases to 350 mmHg (at an altitude of about 6100 meters) while if the subject was breathing **100 % O_2** , it is reached when the atmospheric pressure decreases to 120 mmHg (at an altitude of about 13700 meters).

ACUTE MOUNTAIN SICKNESS

This is a condition that may occur in some individuals when they ascend to high altitudes for the first time. It occurs within 8 - 24 hours and lasts for 4-8 weeks. Its symptoms include *headache, dizziness, irritability, insomnia, fatigue, dyspnea, palpitation, anorexia, nausea and vomiting*. Its cause is probably **cerebral edema** (which is often produced secondary to V.D. of the cerebral vessels that occurs as a result of the low arterial P_{O_2}) because the symptoms markedly improve when the cerebral edema is treated.

ACCLIMATIZATION MECHANISMS

The compensatory mechanisms involved in acclimatization usually start within *one week*. They aim at increasing O_2 delivery to the tissues, and they include the following :

1. Increase of the pulmonary ventilation

This occurs as a result of stimulation of the respiratory centre by signals discharged from the **peripheral chemoreceptors** (which are excited when the arterial P_{O_2} drops below 60 mmHg). The initial response is relatively

small because the resulting hyperventilation washes CO_2 in the expired air resulting in **alkalosis** (which tends to inhibit the respiratory centre). However, within a few days ventilation markedly increases due to :

- a- *Correction of the alkalosis* through excessive excretion of HCO_3^- by the kidneys in the urine (**so the urine pH in high altitudes is alkaline**).
- b- *Stimulation of the central chemoreceptors by the lowered brain pH* (which is produced as a result of development of lactic acidosis, as well as shift of HCO_3^- from the brain to the plasma).

2. Increase of the blood O_2 - carrying capacity

This occurs as a result of *stimulation of erythropoiesis* under the effect of the *erythropoietin hormone* (which is secreted by the kidneys in response to O_2 lack). The red cell count increases up to 8 million / mm^3 (= *physiological polycythaemia*) and the Hb content may increase by 50 % (which increases the O_2 -carrying capacity of the blood) and in addition, the *haematocrit value increases up to 60 % and the blood volume by 20 – 30 %*.

3. Increase of the circulatory rate

Signals from the peripheral chemoreceptors stimulate the vasomotor centre, resulting in *tachycardia and an increase of both the cardiac output and arterial blood pressure*. In addition, *peripheral V.D. and angiogenesis* (= formation of new capillaries) also occur under the effect of O_2 lack. All these effects increase the blood flow to the tissues.

4. Increase of O_2 liberation at the tissues

This is produced through *stimulation of 2-3 DPG synthesis* in the red blood cells at high altitudes, which facilitates O_2 liberation from HbO_2 by shifting the O_2 -Hb dissociation curve to the right (page 70). *2-3 DPG antagonizes the effect of alkalosis* (which tends to shift the O_2 -Hb dissociation curve to the left) and produces *a net increase of the P_{50}* (page 69).

5. Cellular compensatory changes

In response to the low arterial PO_2 , all the following increase in the cells :

- a- The mitochondria (the site of oxidative reactions).
- b- The myoglobin content in skeletal muscles.
- c- The oxidative enzymes (specially the cytochrome oxidase enzyme).

**** Role of the kidneys in high altitudes :**

1. Secretion of *erythropoietin* (which stimulates red cell formation).
2. Excretion of HCO_3^- (which corrects the developed alkalosis).

Colour of the skin in various types of hypoxia

1. **In hypoxic hypoxia**, there is *cyanosis* (i.e. the skin is *bluish*) because of presence of abnormally great amounts of reduced Hb in the blood.
2. **In anaemic hypoxia**, the skin is *pale*, except in CO poisoning in which the skin is *cherry red* (which is the colour of carboxyHb)
3. **In stagnant hypoxia**, there is *cyanosis* (i.e. the skin is *bluish*) because of presence of abnormally great amounts of reduced Hb in the venous blood as a result of blood stagnation in the tissues.
4. **In histotoxic hypoxia**, the skin is *red* because the amount of oxyHb in the arterial blood is normal *while that in the venous blood is increased*

CYANOSIS**DEFINITION OF CYANOSIS**

Cyanosis is a *blue discolouration of the skin and mucous membranes* due to presence of an abnormally great amount of **reduced Hb** in the superficial capillaries. It is easily seen in the nail beds, mucous membranes, and the areas that have thin skin e.g. the ear lobes, lips and fingers.

THRESHOLD OF CYANOSIS

This is the minimal concentration of reduced Hb in the capillary blood that leads to appearance of cyanosis. Under normal conditions, the threshold of cyanosis is **5 gm reduced Hb / 100 ml of capillary blood**.

**** Cyanosis does not occur normally because the amount of reduced Hb in the capillary blood is calculated to be only 2.1 gm / 100 ml as follows :**

- a- The arterial blood contains 3 % reduced Hb, and since the Hb concentration in the blood averages 15 gm %, then the amount of reduced Hb in the arterial blood = $15 \times 3 / 100 = 0.45 \text{ gm / 100 ml}$.
- b- The venous blood contains 25 % reduced Hb, so the amount of reduced Hb in the venous blood = $15 \times 25 / 100 = 3.75 \text{ gm / 100 ml}$.
- c- The amount of reduced Hb in the capillary blood is the average of the amounts present in the arterial and venous blood =
 $[0.45] + [3.75] \div 2 = 2.1 \text{ gm / 100 ml blood}$

CAUSES OF CYANOSIS

1. **Hypoxic hypoxia** (because both the arterial and venous blood contain abnormally greater amounts of reduced Hb).
2. **Stagnant hypoxia** (due to much reduction of Hb in the venous blood).
3. **Asphyxia** (in which there is both hypoxia and hypercapnia).

**** In high altitudes, the threshold of cyanosis is more easily reached** because the total amount of Hb is markedly increased.

**** Cyanosis does not occur in anaemic hypoxia** (because the total amount of Hb is decreased) specially in CO poisoning (because of the cherry red colour of carboxyHb).

**** Cyanosis does not also occur in histotoxic hypoxia** (because the venous blood contains a smaller amount of reduced Hb than normal).

**** Normal subjects frequently develop cyanosis in cold weather** due to slowing of the blood flow in the skin as a result of V.C.. However cyanosis may be **absent in very cold weather** because the release of O₂ from Hb in this case is much decreased (due to reduction of the tissue activity and shift of the O₂-Hb dissociation curve to the left). In the latter condition, the skin colour may be **reddish** because the severe V.C. leads to tissue ischaemia, and this increases the formation of metabolites, which accumulate and lead to V.D. (resulting in the reddish colour of the skin).

DEPTH OF CYANOSIS

There is usually no relation between the severity of the condition and the depth of cyanosis. This is shown in the following examples :

1. In cases of hypoxic hypoxia, **bleeding improves cyanosis** (due to loss of reduced Hb) although the condition becomes worse (due to loss of HbO₂).
2. In high altitudes, persons may be very deeply cyanosed although they live almost normally (because the blood contains sufficient amounts of oxyHb).

TYPES OF CYANOSIS

1. **Central cyanosis** : This is **generalized** (allover the body) and it occurs in cases of hypoxic hypoxia that are due to central causes specially :
 - a- Cardiac diseases e.g. congestive heart failure and various septal defects.
 - b- Diseases that interfere with ventilation or gas exchange in the lungs.
2. **Peripheral cyanosis** : This is **localized** to the areas of reduced blood flow e.g. due to V.C., as occurs in **Raynaud's disease** (page 80).

****** Peripheral cyanosis can be differentiated from central cyanosis simply by *warming the skin*. This procedure leads to *V.D. which improves peripheral cyanosis but does not affect central cyanosis or renders it deeper*.

****** Cyanosis is differentiated from skin contusions simply by *applying pressure to the discoloured area*. This procedure *does not affect contusions but improves cyanosis (because it squeezes blood out from the capillaries)*.

FACTORS THAT AFFECT CYANOSIS

1. **Capillary factors** : Factors that increase the number of open capillaries or their diameters e.g. (heat, CO₂ and acid metabolites) increase the depth of central cyanosis but improve peripheral cyanosis (see above).
2. **Skin thickness** : Cyanosis is deeper in thin skin areas and vice versa.
3. **Skin pigmentation** : Cyanosis is altered by skin pigmentation, whether physiological (e.g. in yellow races) or pathological (e.g. in jaundice). In dark races, cyanosis in the skin is masked, *but it can still be detected in the mucous membranes*.
4. **Blood composition** : The presence of abnormally great amounts of *met-Hb* produces a cyanotic-like colour. Other abnormalities in the blood composition also alter the depth of cyanosis (e.g. lipaemia and leukaemia).
5. **The amounts of reduced Hb and oxyHb** : Cyanosis becomes deeper if the amount of reduced Hb is increased or the amount of oxyHb is decreased, and vice versa.

OXYGEN THERAPY

USES OF OXYGEN THERAPY IN HYPOXIA

1. Oxygen therapy is *useful in cases of hypoxic hypoxia, except in cases of right to left cardiac shunts* (page 79) in which blood bypasses the lungs.
2. Oxygen therapy is *almost not useful in anaemic, stagnant and histotoxic hypoxia*, in which it only increases the physically dissolved O₂ in the blood.
3. Oxygen therapy *improves cyanosis and is helpful in CO poisoning*.

OXYGEN TOXICITY (HYPEROXIA)

(A) When using 100 % oxygen at one atmospheric pressure

In this case, the administration of O₂ for more than 8 hours causes *tracheobronchial irritation, substernal stress, nasal congestion, sore throat and coughing*, and on exposure for 24-48 hours, *lung damage also occurs*.

(B) When using 100 % oxygen at high atmospheric pressures

This is known as hyperbaric oxygen. It accelerates the onset of the symptoms of O_2 toxicity (see above) and, in addition, it causes *twitching of the muscles, ringing in the ears, dizziness, convulsions and coma*.

Hyperbaric oxygenation is useful in the following conditions :

- 1- Certain cases of cardiac surgery.
- 2- Gas gangrene.
- 3- CO poisoning (and may be also cyanide poisoning).

****** The exposure to hyperbaric O_2 shouldn't exceed 5 hours and at less than 3 atmospheric pressures, due its effects (see above) and dangers (see below),

DANGERS OF OXYGEN THERAPY

Prolonged exposure to pure O_2 (specially hyperbaric O_2) causes :

1. Thickening of the respiratory membrane (= *alveolo-capillary block*)
2. *Decreased formation of the surfactant* (page 33)..
3. *Decrease of the ATP content in the brain, liver and kidneys* (in rats).
4. *Retrolental fibroplasia* (formation of opaque vascular tissue in the eyes).
5. *Bronchopulmonary dysplasia* (a condition characterized by development of multiple lung cysts and densities). It frequently occurs (and also retrolental fibroplasia) in *premature infants who receive O_2 in incubators*.
6. *Acidosis (due to excessive CO_2 dissolution in the blood)* : This occurs because the tissues obtain their O_2 needs from the increased physically dissolved O_2 and *not from oxyHb* (which decreases the amounts of reduced Hb and K^+ that can carry CO_2 in the chemical form, pages 73 and 74).
7. Oxygen therapy may be fatal in the following conditions :

a- Severe hypercapnia : When this occurs (e.g. in chronic lung diseases that predispose to pulmonary failure), *the increased arterial P_{CO_2} depresses rather than stimulates respiration*, and the *resulting hypoxaemia becomes the main stimulant of the respiratory centre*. Oxygen therapy in these cases abolishes this hypoxic respiratory drive, which may lead to respiratory arrest and death

b- Deep anaesthesia : During deep anaesthesia, *the sensitivity of the central chemoreceptors to CO_2 is decreased*. Accordingly, respiration is depressed, and the *resulting hypoxaemia becomes the main stimulant of the respiratory centre*. Oxygen therapy in these cases abolishes this hypoxic respiratory drive, which may lead to respiratory arrest and death.

CHAPTER 9

PHYSIOLOGY OF DEEP SEA DIVING (EFFECTS OF INCREASED BAROMETRIC PRESSURE)

Under the normal atmospheric pressure at the sea level (= 760 mmHg), the human body contains about 1000 ml of N_2 dissolved in the various body fluids and tissues. N_2 is an *inert gas* i.e. it plays no role in metabolism and is neither utilized nor produced by the body. Its function is only *to dilute atmospheric oxygen and to keep the alveoli distended*.

One of the major problems that face divers is the high pressure of water (*about 1 atmosphere every 10 meters of depth in sea water*) which compresses the chest and makes breathing difficult.

For this reason, users of the **SCUBA** (= *Self-Contained Underwater Breathing Apparatus*) and workers in **caissons** (= water-tight chambers designed for working under water) *breathe air under high pressure to resist the high water pressure. In all compressed air equipments, the pressure of the inspired gas is matched to the pressure of the surroundings.*

While under water, *breathing air (which contains about 20 % O_2) is preferred to pure O_2* to avoid O_2 toxicity (page 86), and CO_2 is routinely removed from the breathed air to prevent its accumulation in the body.

The increased P_{O_2} and P_{N_2} in the inspired air increases the dissolved amounts of these gases in the body. The *dissolved O_2 is used* by the tissues while *N_2 is not used and remains dissolved in the tissues*, specially the *adipose tissue* (because N_2 is 5 times more soluble in fat than in water). This dissolved N_2 may produce problems to the divers such as *narcosis and decompression sickness* (see below)

N_2 and the trace gases (argon, krypton, neon, xenon and helium) are *physiologically inert at the normal atmospheric pressure*. However, *under high pressures, they exert an anaesthetic effect* (probably by dissolving in the nerve cell membranes and affecting the ionic diffusion across them).

NITROGEN NARCOSIS

This condition occurs when *breathing air* at a pressure of 4 - 5 atmospheres i.e. at depths of *30 - 40 meters under sea water*. The increased P_{N_2} in

the blood produces **euphoria** (sense of pleasant excitement and well-being). At greater depths, symptoms similar to those of **alcohol intoxication** appear and the intellectual functions are impaired while the manual skills are maintained. However, at more greater depths, the **manual skills are also lost** (leading to incoordination of movements) and **narcosis** (i.e. tendency to sleep) occurs, which often terminates by coma.

How can nitrogen narcosis be avoided ?

Nitrogen narcosis can be avoided (and deeper dives can also be made) **by breathing mixtures of oxygen and helium**. This is because helium is less dissolved in the body fluids than N_2 and also has a smaller molecular weight (so it diffuses out from the tissues faster than N_2). However, it also produces some harmful effects (see next).

The high pressure nervous syndrome (HPNS)

This syndrome results from **helium toxicity**. It usually occurs when breathing mixtures of oxygen and helium at depths exceeding 70 meters, at which the pressure is about 8 atmospheres. Its symptoms include tremors, drowsiness and depression of some EEG activities, but unlike nitrogen narcosis, the intellectual functions are not severely affected while the manual skills are impaired.

DECOMPRESSION SICKNESS (CAISSON'S DISEASE, DYSBARISM OR BARO-TRAUMA)

This is a serious condition that may occur in divers or caisson workers after staying in deep water for sometime. During ascending to the surface, a process of **decompression** occurs (i.e. the surrounding pressure decreases towards the atmospheric pressure), so the P_{N_2} in the alveolar air drops.

If such decompression was gradual (by ascending slowly), the dissolved N_2 in the tissues diffuses gradually into the blood then, in the lungs, it is eliminated in the expired air, and **no harmful effects occur**.

On the other hand, if decompression was rapid (e.g. due to rapid ascent to the surface because of an accident), N_2 escapes from solution rapidly and expands according to **Boyle's law** (page 59) **just as CO_2 comes out of solution when a bottle of soda water is opened**. This leads to **formation of N_2 bubbles in the blood and tissues**, which cause serious effects (see below).

For this reason, the ascent to the surface should be **slow and systematic**

i.e. it must be performed in stages that are determined by special decompression tables which indicate the depths at which the subject should stay and for how long at each depth.

Symptoms of decompression sickness

The symptoms of decompression sickness usually appear 10–30 minutes after returning to the surface, and they include the following :

1. Severe pain, paraesthesia and itching (due to stimulation of the pain receptors in the tissues by the N_2 bubbles). Pain specially occurs around the joints in the upper and lower limbs (so the condition is also called the bends).
2. The N_2 bubbles that *enter the blood stream* obstruct the arteries causing :
 - a- *Neurological symptoms* (due to obstruction of the spinal and cerebral arteries) e.g. dizziness, impaired vision, confusion, unsteadiness, muscle fatigue or paralysis (= *diver's paralysis*) as well as unconsciousness.
 - b- *Dyspnea (chokes)* due to excitation of the pulmonary irritant receptors secondary to blocking of the pulmonary vessels.
 - c- *Angina pectoris or myocardial infarction* due to blocking of the coronary arteries.

Treatment of decompression sickness

The risk of decompression sickness can be decreased by breathing O_2 -helium mixtures during the dive and by ascending slowly to the surface. However, if its symptoms appear, it can be treated by recompression (in *special pressure chambers*) followed by gradual decompression while the person is inhaling O_2 (to accelerate washing out of N_2 from the body).

****** Decompression sickness also occurs in *pilots during rapid ascents in unpressurized airplanes* because the atmospheric pressure drops to 1/3 at a height of 8550 meters, which is the same as happens on ascending from a depth of 20 meters under sea water to the surface (during which the pressure drops from 3 to 1 atmosphere).

AIR EMBOLISM

If a diver breathing from a high-pressure tank *holds his breath and ascends rapidly to the surface*, the air in the lungs expands markedly. This may tear the lungs and rupture the pulmonary veins. The latter drives air into the blood vessels resulting in air embolism (i.e. formation of *air bubbles* in the blood), which may be fatal if these bubbles occlude vital blood vessels). It is to be noted that decompression sickness is a type of air embolism.

Explosive decompression

This is a severe (and often fatal) type of air embolism. It occurs when the external pressure suddenly drops from atmospheric to subatmospheric e.g. if *the wall of a pressurized airplane (or a rocket) is broken at a high altitude*.

AUTHOR'S AVAILABLE BOOKS

- 1- Human physiology for medical students : Endocrine glands and reproduction.
- 2- Human physiology for medical students : Special senses.
- 3- Human physiology for medical students : The cell, Autonomic nervous system and Nerve & Muscle.
- 4- Human physiology for medical students : Blood and body fluids.
- 5- Human physiology for medical students : Kidney, Electrolyte and Acid-Base balance.
- 6- Human physiology for medical students : Central nervous system (CNS).
- 7- Human physiology for medical students : Circulation (CVS).
- 8- Human physiology for medical students : Respiration.
- 9- Human physiology for medical students : Digestion (GIT).
- 10- Human physiology for medical students : Energy metabolism.
- 11- Oral and written questions and answers (2 volumes).
- 12- M.C.Q.s and answers (2 volumes).
- 13- A summarized guide to circulation.
- 14- A summarized guide to CNS.



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